Official Protocol Title:	A Phase III Placebo-controlled Clinical Trial to Study the Tolerability, Immunogenicity and Efficacy of V501 in 16- to 26-year-old Japanese men
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Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or Merck)
One Merck Drive
P.O. Box 100
Whitehouse Station, NJ 08889-0100, U.S.A.

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

TITLE:

A Phase III Placebo-controlled Clinical Trial to Study the Tolerability, Immunogenicity and Efficacy of V501 in 16- to 26-year-old Japanese men

EudraCT NUMBER: Not Applicable

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1.0 TRIAL SUMMARY

Abbreviated Title	Tolerability, immunogenicity and efficacy trial of V501 in Japanese men
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	Placebo
Route of administration	Intramuscular
Trial Blinding	Double-blind
Treatment Groups	V501 or placebo
Number of trial subjects	Approximately 1,100 subjects will be enrolled. The enrollment of approximately 10% of Men who have sex with men (MSM) is targeted
Estimated duration of trial	The sponsor estimates that the trial will require approximately 50 months (Study Period for Clinical Trial Notification (CTN): From May 2013 to Dec 2017) from the time the first subject signs the informed consent until the last subject's last visit.
Duration of Participation	Each subject will participate in the trial for approximately 36 months, from the time the subject signs the Informed Consent Form (ICF) through the final contact. Each subject will be receiving 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 approximately 30 months.
Randomization Ratio	Subject will be randomized in 1:1 ratio to V501 or placebo.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a randomized, placebo-controlled, parallel-group, multi-site, double-blind trial of V501 [quadrivalent HPV (Type 6, 11, 16 and 18) L1 Virus-like Particle (VLP) vaccine] in healthy male subjects to be conducted in conformance with Good Clinical Practices.

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.

The primary analysis is case driven and will be conducted after at least 18 primary efficacy cases have been observed. In addition, an interim analysis will be performed when at least 11

primary efficacy cases have been observed. Results of the interim analysis will be reviewed by external Data Monitoring Committee (DMC). If the results meet the criteria (see Section 8.2.8 for the detail of criteria), DMC will make recommendation to the Sponsor to unblind and conduct the primary efficacy analysis with at least 11 primary efficacy cases. If not, the primary analysis will be conducted when 18 primary efficacy cases have been observed. Since the primary efficacy analysis will be conducted prior to completion of the study irrespective of the results of interim analysis, the remainder of the study is considered as an extension. The purpose of the extension is to collect data on the longer-term efficacy, tolerability, and immunogenicity of the vaccine.

The interim analysis will be conducted by the unblinded statistician. The clinical, statistical and data management study personnel at the Sponsor who are involved with study conduct will be blinded to subject vaccination group allocations during the process of interim analysis, and remain blinded until either the DMC recommends to unblind or 18 cases of the primary efficacy endpoint have been observed and the database is unblinded for the analysis. Laboratory personnel, the pathology panel, and the investigators, site personnel and subjects will remain blinded to whether subjects received V501 or Placebo throughout the entire study period.

2.2 Trial Diagram

The trial design is depicted in Figure 1.

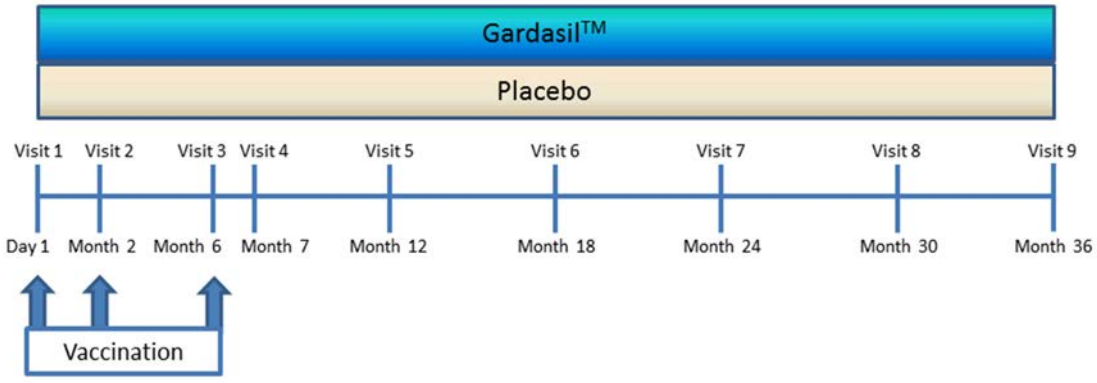

Figure 1 Trial Design

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

(1) **Objective:** To demonstrate that a 3-dose regimen of V501 will reduce the combined incidence of HPV 6-, 11-, 16- or 18-related persistent infection detected in samples from two or more consecutive visits (±1 month visit windows) 6 month or longer apart compared with placebo in 16- to 26-year-old Japanese men who are seronegative at Day 1 and polymerase chain reaction (PCR) negative Day 1 through Month 7 to the relevant HPV type.

Hypothesis: A 3-dose regimen of V501 to 16- to 26-year-old Japanese men who are seronegative at Day 1 and PCR negative Day 1 through Month 7 to the relevant HPV type reduces the combined incidence of HPV 6-, 11-, 16- or 18-related persistent infection detected in samples from two or more consecutive visits (±1 month visit windows) 6 month or longer apart compared with placebo. The statistical criterion for success requires that the lower bound of the two-sided 95% confidence interval for the vaccine efficacy excludes 0%.

(2) **Objective:** To demonstrate that a 3-dose regimen of V501 to 16- to 26-year-old Japanese men is generally well tolerated.

3.2 Secondary Objective(s) & Hypothesis(es)

(1) **Objective**: To demonstrate that a 3-dose regimen of V501 will reduce the combined incidence of HPV 6-, 11-, 16- or 18-related persistent infection, condyloma acuminata, penile/perianal/perineal intraepithelial neoplasia (PIN), penile, perianal or perineal cancer compared with placebo in 16- to 26-year-old Japanese men who are seronegative at Day 1 and PCR negative Day 1 through Month 7 to the relevant HPV type.

Hypothesis: A 3-dose regimen of V501 to 16- to 26-year-old Japanese men who are seronegative at Day 1 and PCR negative Day 1 through Month 7 to the relevant HPV type reduces the combined incidence of HPV 6-, 11-, 16- or 18-related persistent infection, condyloma acuminata, penile/perianal/perineal intraepithelial neoplasia (PIN), penile, perianal or perineal cancer compared with placebo. The statistical criterion for success requires that the lower bound of the two-sided 95% confidence interval for the vaccine efficacy exclude 0%.

3.3 Exploratory Objective(s)

(1) **Objective**: To evaluate the anti-HPV 6, 11, 16 or 18 immune responses generated by V501 in all subjects, Heterosexual Men (HM) subjects group and Men who have Sex with Men (MSM) subjects group, respectively.

(2) **Objective**: To evaluate that a 3-dose regimen of V501 will reduce the combined incidence of HPV 6-, 11-, 16- or 18-related condyloma acuminata compared with placebo in 16- to 26-year-old Japanese men who are seronegative at Day 1 and PCR negative Day 1 through Month 7 to the relevant HPV type.

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 June 2012, V501 was approved and marketed under the names GARDASIL™/SILGARD™ in over 120 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 5 years postvaccination onset [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]. However, 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 finding in overseas clinical trial, V501-020, to Japanese young men, via the demonstration of the efficacy against HPV type 6, 11, 16 or 18 persistent infection in Japanese young men. Considering the comparison between this trial data and previous trial data (V501-020), 16 to 26 years old HM and MSM are selected as this trial population in a manner consistent with Protocol V501-020. The enrollment of approximately 10% of MSM subject is targeted in this trial. Please note “10%” is a target number considering the challenging nature of MSM enrollment in Japan from operational aspect. In addition, subjects will be enrolled regardless of the history of circumcision.

Details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying IB and Informed Consent documents.

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 effectiveness of an investigational vaccine.

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 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 many countries including Japan will be used in this trial. In addition, placebo (including AAHS 225 µg) will be included in this trial to demonstrate the efficacy of V501.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

The primary efficacy endpoint is the incidence of HPV 6-, 11-, 16- or 18-related persistent infection. This endpoint was chosen based on the finding from overseas V501 phase III trial in men (Protocol V501-020) that HPV related persistent infection is a predictor of HPV related diseases in men. In Protocol V501-020, V501 showed prophylactic efficacy against HPV 6-, 11-, 16- or 18-related condyloma acuminata as well as HPV 6-, 11-, 16- or 18-related persistent infection in 16- to 26-year-old men. Additionally, the composite incidence of HPV 6-, 11-, 16- or 18-related persistent infection and condyloma acuminata, PIN, penile, perianal or perineal cancer are investigated as for the secondary endpoint.

Subjects will undergo sampling from the penis, scrotum, and perianal region using a nail file followed by a wetted DACRON™ swab system for HPV PCR testing. Also, an intra-anal swab specimen for HPV PCR will be collected. These swabs will be tested for detection of HPV types 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 by PCR assay. PCR analysis of the swabs will be used to identify subjects who have an active HPV infection at enrollment and to determine persistent HPV infection endpoints.

A detailed genitourinary and perianal inspection will be performed. If a lesion observed at Day 1 is assessed to be possibly, probably or definitely HPV-related or of unknown etiology, then the subject should be excluded from the study. All new (after Day 1) genitourinary and perianal lesions judged by the investigator to be possibly, probably, or definitely HPV-related, or any lesion whose etiology is not known will be biopsied. If multiple lesions are observed (after Day 1), then lesions of each representative morphology will be biopsied. If more than one anatomic location is affected, then a lesion from each location will be biopsied.

Tissues obtained from biopsy will be analyzed by HPV Thinsection PCR assay and by a consensus diagnosis from the HPV vaccine Program Pathology Panel to determine clinical disease efficacy endpoints.

4.2.3.2 Immunogenicity Endpoints

Anti-HPV 6, 11, 16 or 18 will be analyzed as the indicator of immune responses to each vaccine components.

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

Findings from the V501 phase III trial in men (Protocol V501-020) indicate that antibody responses to the vaccine are markedly reduced in MSM subjects compared to HM subjects. Therefore, immunogenicity of V501 will be summarized separately in these 2 populations in addition to all subjects group.

4.2.3.3 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.

4.2.3.4 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on DNA (blood) specimens collected 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. For instance, exploratory pharmacogenetic (PGt) studies may be performed if significant Pharmacokinetic/Pharmacodynamic (PK/PD) relationships are observed or adverse events are identified. Genomic markers of disease may also be investigated. Such retrospective pharmacogenetic studies will be conducted with appropriate biostatistical design and analysis and compared to PK/PD results or clinical outcomes. Any significant PGt relationships to outcome would require validation in future clinical trials. The overarching goal is to use such information to develop safer, more effective drugs, and/or to ensure that subjects receive the correct dose of the correct drug 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.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Healthy Male subjects between the ages of 16 and 26 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 ages of 16 years and 0 days and 26 years and 364 days.
2. Fully understand (or, for minor subjects, parent/legal guardian and subject) study procedures, alternative treatments available, the risks involved with the study, and voluntarily agrees to participate by giving written informed consent. The subject may also provide consent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.

3. Agree to provide study personnel with a primary telephone number as well as an alternate telephone number for follow-up purposes
4. Have no clinical evidence of gross genital lesion suggesting sexually-transmitted disease and no clinically present external genital warts.
5. *Show no temperature ≥37.5°C (oral) within 24 hours prior to vaccinations.
6. *Agree to refrain from sexual activity (including vaginal and anal penetration and any genital contact) for 2 calendar days prior to any scheduled visit that includes sample collection, to avoid detection of viral DNA which has been deposited in the male genital area during sexual intercourse and is not the result of ongoing infection.
7. a) For HM: Subjects must be a heterosexual male, who has had exclusively female sexual partners, and has 1 to 5 lifetime female sexual partners at the time of enrollment.

   b) For MSM: Subjects must identify themselves as a man who has sex with men, must have engaged in either insertive or receptive anal intercourse or oral sex with another male sexual partner within the past year, and have 0 to 5 lifetime male and/or female sexual partners at the enrollment.

   For protocol purposes, a female sexual partner is defined as a woman with whom the subject has engaged in vaginal intercourse. For protocol purposes, a male sexual partner is defined as a man with whom the subject engaged in insertive or receptive anal intercourse.

For items with an asterisk (*), if the subject does not meet these inclusion criteria, the Day 1 visit be rescheduled for a time when these criteria can be met.

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 or studies involving collection of genital specimens.
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.
4. Has history of external genital warts, or has clinically present external genital warts at Day 1.
5. Has history of severe allergic reaction (e.g., swelling of the mouth and throat, difficulty breathing, hypotension or shock) that required medical intervention.
6. Is allergic to any vaccine component, including aluminum, yeast, or BENZONASE™ (nuclease, Nycomed [used to remove residual nucleic acids from this and other vaccines]).
7. 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.

8. 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.
9. 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.
10. Has known thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injections.
11. 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.
12. 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.
13. Is unlikely to adhere to the study procedures, keep appointments, or is planning to relocate during the study.

For items with an asterisk (*), if the subject does not meet these exclusion criteria, the visit be rescheduled for a time when these criteria can be met.

5.2 Trial Treatments

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

Table 1 Trial Vaccination

Study Vaccine	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
V501	0.5 mL	3	Intramuscular injection	Day 1, Month 2 and Month 6	Investigational
Placebo (including AAHS 225µg)	0.5 mL	3	Intramuscular injection	Day 1, Month 2 and Month 6	Placebo-comparator

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

5.2.1 Dose Selection

5.2.1.1 Dose Selection

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

5.2.3 Trial Blinding/Masking

A double-blind/masking technique will be used. V501 and placebo will be packaged identically so that blind/masking is maintained. The subject, the investigator and Sponsor personnel or delegate(s) who are involved in the treatment or clinical evaluation of the subjects are unaware of the group assignments.

The SPONSOR personnel who are involved with study conduct will be unblinded to subject vaccination group assignments when the database is unblinded for the primary efficacy analysis. The primary efficacy analysis is case driven and may be conducted prior to the end of study. Therefore, the database may be unblinded during the study. However, laboratory personnel, the pathology panel, and the investigators, site personnel and subjects will remain blinded to whether subjects received V501 or Placebo throughout the entire study period.
See Section 7.1.4.2, Blinding/Unblinding, for a description of the method of unblinding a subject during the trial, should such action be warranted.

5.3 Randomization or Treatment Allocation

Randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are 2 vaccination arms. Subjects will be assigned randomly in an 1:1 ratio to V501 and placebo, respectively.

5.4 Stratification

Randomization will be stratified according to the following factors:

1. HM or MSM

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

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

To reduce their potential interference with the evaluation of the immunologic response and reactogenicity of the study vaccine or placebo, 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 and should not be administered during the vaccination series or at any other time during the study, if at all possible. 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 is “permanent”. Once a subject is discontinued, he/she shall not be allowed to enroll again.

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 that 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 overall trial ends when the last subject completes the last trial visit, discontinues from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator).

5.11 Clinical Criteria for Early Trial Termination

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

6.0 TRIAL FLOW CHART

Visit Number:	1	2	3	4	5	6	7	8	9
Scheduled Day/Month.:	Day 1	Month 2	Month 6	Month 7	Month 12	Month 18	Month 24	Month 30	Month 36
Visit Window[1]:		2 months after Day 1, ±3 weeks	6 months after Day 1, ±4 weeks	3 to 7 weeks after Month 6	12, 18, 24, 30 or 36 months after Day 1, ±4 weeks				
Administrative Procedures									
Informed Consent	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	X	X	X
Sexual History	X	X	X	X	X	X	X	X	X
Concomitant Medication Review[2]	X	X	X	X	X	X	X	X	X
Vaccine Allocation/Randomization	X								
V501 /Placebo Administration	X	X	X						
Clinical Procedures/Assessments									
Anogenital Physical Examination	X								
Vital Signs (height, weight, oral temperature, sitting pulse, blood pressure and respiration)[3]	X	X	X						
Provide Vaccination Report Card (VRC)	X	X	X						
Review and Collect VRC data		X	X	X					
Adverse Events Monitoring	X	X	X	X	X	X	X	X	X
Laboratory Procedures/Assessments									
Genitourinary examination for external genital lesions	X			X	X	X	X	X	X
Penile/glans penis file and wetted swab for HPV PCR [4]	X			X	X	X	X	X	X
Scrotal file and wetted swab for HPV PCR [4]	X			X	X	X	X	X	X
Perianal examination for external genital lesions	X			X	X	X	X	X	X
Perineal/perianal file and wetted swab for HPV	X			X	X	X	X	X	X

Visit Number:	1	2	3	4	5	6	7	8	9
Scheduled Day/Month.:	Day 1	Month 2	Month 6	Month 7	Month 12	Month 18	Month 24	Month 30	Month 36
Visit Window[1]:		2 months after Day 1, ±3 weeks	6 months after Day 1, ±4 weeks	3 to 7 weeks after Month 6	12, 18, 24, 30 or 36 months after Day 1, ±4 weeks				
PCR[4]									
Intra-anal wetted swab for HPV PCR [4]	X			X	X	X	X	X	X
External genital lesion biopsy (if indicated) [5]		X	X	X	X	X	X	X	X
Serum for Anti-HPV [6]	X			X					X
STI Testing (local laboratory testing, if clinically indicated) [7]	X	X	X	X	X	X	X	X	X
Blood (DNA) for Future Biomedical Research [8]	X								

1 To calculate visit windows, assume 1 month equals 30 days and 1 week equals 7 days. With regard to protocol study visit windows, the following situations require consultation between the investigator and the SPONSOR and written documentation of the collaborative decision: a subject needs to be scheduled earlier than the start of a visit window, the study site is considering skipping a visit, or a study site needs significant guidance on scheduling visit windows.

2 See Section 5.5 for prerequisites for medications and non-study vaccines.

3 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.

4 Type-specific HPV Polymerase Chain Reaction (PCR) testing to be performed at the SPONSOR-designated Central Laboratory. Swabs must be shipped as specified by the SPONSOR/Central Laboratory.

5 Processed and analyzed at Central Laboratory.

6 Serum for anti-HPV measurements may be collected after the genitourinary/perianal examination, but must be collected before vaccination. Serum (including Reference Serum) must be shipped as specified by the SPONSOR/Central Laboratory.

7 Sexually transmitted infection (STI) tests, including HSV, syphilis, and HIV, may be performed at any visit as needed.

8 Informed consent for future biomedical research samples must be obtained before the DNA sample is collected. DNA sample for analysis (8.5-mL blood sample) should be collected before vaccine administration, on Day 1 (or with the next scheduled blood draw, as soon as consent is obtained) and on randomized subjects only.

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 must obtain documented consent from each potential subject 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.

In addition, demographics and substance use will be collected in the data collection system, as discussed in the Electronic Case Report Form (eCRF) Entry Guideline.

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 after the subject provides written informed consent.

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. At Visit 1 (Day 1), the subject's lifetime genitourinary history and 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 Sexual History

A sexual history will be obtained by the investigator or qualified designee. At Visit 1 (Day 1), the subject's lifetime number of female and/or male sexual partners and age of first sexual intercourse will be collected. After Visit 1, the subject's sexual activity including the number of new females and/or males with which the subject engaged in sexual intercourse (for females, insertive vaginal intercourse; for males insertive or receptive anal intercourse) will be collected.

7.1.1.6 Prior and Concomitant Medications Review

7.1.1.6.1 Prior Medications

The investigator or qualified designee will review prior medication use, and record prior medication taken by the subject before starting 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 non-study 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.

7.1.1.6.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial as described in Section 7.1.1.6.1.

7.1.1.7 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.

7.1.1.8 Assignment of Randomization Number

All eligible subjects will be randomly allocated and will receive a randomization number. The randomization number identifies the subject for all procedures occurring after randomization. Once a 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 randomization number.

7.1.1.9 Study Vaccine Administration

7.1.1.9.1 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, semi-translucent suspension when thoroughly mixed. If the appearance is otherwise, do not administer, and contact the SPONSOR immediately

7.1.1.9.2 Study Vaccine Administration

At each vaccination visit, subjects will receive V501 or placebo 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.

7.1.1.10 Trial Compliance

Administration of trial vaccine will be witnessed by the investigator and documented in the subject's chart.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Anogenital Physical Examination

A physical examination will be performed prior to the external genital lesion examination. A physical examination details will be documented in the subject's chart and any medical conditions including will be documented in the data collection system.

7.1.2.2 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.

7.1.2.3 Vaccination Report Card (VRC)

Each subject will receive a VRC at the study vaccination visit. On the VRC, 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 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 subject and must be signed and dated by the subject to confirm the accuracy of the recorded information. The subject 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. 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. Only the subject can make corrections to his information on the VRC. 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 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.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below.

7.1.3.1 External Genital Lesion Examination

The external genital lesion examination should be completed prior to any specimen collection.

Equipment

The minimal equipment needed to perform the genital lesion inspection includes:

- Good light source
- Magnifying apparatus (hand-held magnifying glass of 4x to 5x power)
- Nonsterile gloves
- Optional: colposcope at low power magnification (2x to 4x)

7.1.3.1.1 Procedure for Penile and Scrotal Examination

1) The examiner should inquire as to whether the subject has shaved their genital region and/or applied any post-shave lotion or lubricants within 24 hours prior to the visit.

2) The examiner should inquire as to whether the subject has noticed any bumps or lesions or unusual symptoms (e.g., etching, dyspareunia, or dysuria). Begin with the inspection of the penile shaft, glans penis and urethral meatus, noting and recording evidence of abnormalities, including any abnormalities of the skin, rashes, minor lacerations, or bruises, etc.

3) The entire penis is to be palpated, region by region, for apparent cutaneous and subcutaneous lesions or wart-like growths.

4) After completing the inspection of the penis, continue with a careful examination is to be performed using the hand-held magnifying glass and/or colposcope and should include the penile shaft, glans penis, and urethral meatus, and scrotum.

5) At the investigator's discretion, low power magnification with the colposcope may be used for better visualization of an identified lesion.

6) Acetic acid is not be used routinely. It may be used for confirmation of a suspected lesion.

7.1.3.1.2 Procedure for Perineal/Perianal Examination

1) The examiner should inquire as to whether the subject has noticed any bumps or lesions or unusual symptoms (e.g., etching, dyspareunia)

2) Inspect the anus, perianal and perineal areas for the presence of anogenital warts.

3) The perianal and perineal regions are to be palpated, for apparent cutaneous and subcutaneous lesions or wart-like growths.

4) The examiner should spread the contiguous skin by the use of his/her thumbs, and note the condition of the anus.

5) The examiner is to be performed using the hand-held magnifying glass and/or colposcope and should include the perianal and anal region.

6) At the investigator's discretion, low power magnification with the colposcope may be used for better visualization of an identified lesion.

7) Acetic acid is not be used routinely. It may be used for confirmation of a suspected lesion.

7.1.3.2 Swab for HPV PCR

After the completion of external genital lesion examination, swab specimens from the penile shaft, scrotum, perineal, perianal and intra-anal region will be collected. Swabs will be tested for detection of HPV types 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59. In addition to this testing, swabs may be tested for other HPV types. HPV type 6, 11, 16 and 18 will be analyzed by type-specific multiplex (L1, E6 and E7 gene detection) PCR assay.

7.1.3.2.1 Penile/Glans Penis File and Wetted Swab for HPV PCR

1) In order to prepare the subject for the specimen collection with nail file, the examiner should demonstrate a nail file (not kept in sterile condition) prior to the procedure, and ask the subject to rub it on his hands.

2) Remove the nail file from the packaging; remove the DACRON™ swab from the packaging, then twist the top off of the sterile saline ampule, and wet the entire head of the DACRON™ swab with the sterile saline, but do not over moisten. If necessary, squeeze the head of the swab to remove excess liquid (while maintaining sterility), as too much liquid may wash cells off the skin instead of collecting them on the swab. If the swab is dripping saline, it is too wet. Only one file and one swab are to be used in the penile sampling.

3) In circumcised men, the examiner wearing gloves should hold the tip of the penis with the thumb and index finger of the non-dominant hand. The file should be held in the dominant hand and in a tight up and down motion (or back and forth motion), gently move the file over the left and right side of the penile shaft, encompassing the whole shaft, and then gently rub the glans. Sufficient pressure should be applied in order to cause blanching of the skin. If blanching is not observed, pressure should be increased in order to collect the required DNA. Subsequently, the examiner should hold the swab in the dominant hand and in a tight up and down motion, gently swab the shaft and glans following the same route. As with the file, sufficient pressure should be used with the DACRON™ swab to blanch the skin while moving it over the area of loosened cellular debris. The swab should also be twisted or rotated in order to increase surface area exposure for collection of cellular debris.

4) In uncircumcised men, the examiner wearing gloves should hold the tip of the penis with the thumb and index finger of the non-dominant hand. The file should be held in the dominant hand and in a tight up and down motion (or back and forth motion), gently move the file over the left and right side of the penile shaft, including the outer foreskin. The examiner should retract the foreskin, and hold the penis with the thumb and the index finger, and gently rub the file over the glans. Sufficient pressure should be applied in order to cause blanching of the skin. If blanching is not observed, pressure should be increased in order to collect the required DNA. Then follow with a wetted swab and rub the penile shaft, the outer foreskin, and then retract the foreskin, and swab the glans, following the same route as the file. As with the file, sufficient pressure should be used with the DACRON™ swab to blanch the skin while moving it over the area of loosened cellular debris. The swab should also be twisted or rotated in order to increase surface area exposure for collection of cellular debris.

5) Discard the file in a Biohazard Sharps Container.

6) Place the swab in an STM vial and break the pre-scored handle. Do not add saline to the STM vial either before or after swabbing.

7) Securely cap the collection/transport tube containing the specimen.

8) Place the appropriate label for the Penile Sample on the STM vial.

7.1.3.2.2 Scrotal File and Wetted Swab for HPV PCR

1) Remove the nail file from the packaging; remove the DACRON™ swab from the packaging, then twist the top off of the sterile saline ampule, and wet the entire head of the DACRON™ swab with the sterile saline, but do not over moisten. If necessary, squeeze the head of the swab to remove excess liquid (while maintaining sterility), as too much liquid may wash cells off the skin instead of collecting them on the swab. If the swab is dripping saline, it is too wet. Only one file and one swab are to be used in the scrotal sampling.

2) With the non-dominant hand, lift and move the penis off of the scrotum, and gently rub the file over the entire scrotum with a tight up and down motion (or back and forth motion), moving from left to right. Sufficient pressure should be applied in order to cause blanching of the skin. If blanching is not observed, pressure should be increased in order to collect the required DNA. It is important to stretch or pull the skin taut in order to allow enough pressure to be applied by the nail file. If necessary, the subject can assist with this activity by holding the skin at the bottom of the scrotum while the file (and subsequently the wetted swab) is moved across the area. The subject should not perform the filing or swabbing procedure.

3) Subsequently, with the non-dominant hand, lift the penis, and gently rub the wetted swab over the entire scrotum with a tight up and down motion, moving from left to right. As with the file, sufficient pressure should be used with the DACRON™ swab to blanch the skin while also be twisted or rotated in order to increase surface area exposure for collection of debris. Only one file and one swab are to be used in the scrotal sampling.

4) Discard the file in a Biohazard Sharps container.

5) Place the swab in an STM vial and break the pre-scored handle. Do not add saline to the STM vial either before or after swabbing.

6) Securely cap the collection/transport tube containing the specimen.

7) Place the appropriate label for the Scrotal Sample on the STM vial.

7.1.3.2.3 Perineal/Perianal File and Wetted Swab for HPV PCR

1) Remove the nail file from the packaging. Remove the DACRON™ swab from the packaging, then twist the top off of the sterile saline ampule, and wet the entire head of the DACRON™ swab, but do not over moisten. If necessary, squeeze the head of the swab to remove excess liquid (while maintaining sterility), as too much liquid may wash cells off the skin instead of collecting them on the swab. If the swab is dripping saline, it is too wet. Only one file and one swab are to be used in the perineal/perianal sampling.

2) If the subject is in the left lateral position, the subject should lift their right leg, so that the perineal area is able to be visualized. Gently rub the file over the right and left side of the perineal and perianal area. It is important to spread the buttocks apart for ample sampling of the perianal region. Sufficient pressure should be applied in order to cause

blanching of the skin. If blanching is not observed, pressure should be increased in order to collect the required DNA. The examiner should gently swab the perineal area. Using the non-dominant hand, the examiner should spread the buttocks to better visualize the perianal area and the anus. The swab should be held in the dominant hand, and starting 3 to 5 cm from the anus, begin swabbing in a circular motion until the entrance of the anus is reached. As with the file, sufficient pressure should be used with the DACRON™ swab to blanch the skin while moving it over the area of loosened cellular debris. The swab should also be twisted or rotated in order to increase surface area exposure for collection of debris.

3) Discard the file in a Biohazard Sharps container.

4) Place the swab in an STM vial and break the pre-scored handle. Do not add saline to the STM vial either before or after swabbing.

5) Securely cap the collection/transport tube containing the specimen.

6) Place the label for the Perianal Sample on the STM vial.

7.1.3.2.4 Intra-anal Wetted Swab for HPV PCR

1) Remove the DACRON™ swab from the packaging, then twist the top off of the sterile saline ampule, and wet the entire head of the DACRON™ swab with the sterile saline.

2) Using the non-dominant hand, the examiner should spread the buttocks to better visualize the perianal area and the anus. The swab should be held in the dominant hand.

3) Once at the entrance to the anus, the contiguous skin should be spread and the swab should be inserted into the anus as far as it will go until resistance is met (generally 5-6 cm), swabbing the inside of the anal canal in a 360º rotating motion 2 to 3 times.

4) Place the swab in an STM vial and break the pre-scored handle. Do not add saline to STM vial either before or after swabbing.

5) Securely cap the collection/transport tube containing the specimens.

6) Place the appropriate label for the Intra-Anal sample on the STM vial.

7.1.3.3 External Genital Lesion Biopsy

After a thorough examination, the investigator's clinical impression should be recorded. If a lesion, in the investigator's opinion, is possibly, probably, or definitely HPV infection-related or the diagnosis is unknown, it should be biopsied for further evaluation. For multiple lesions, select one external lesion to biopsy that is most representative of the morphology or anatomic location, and is most accessible. A second biopsy is indicated, if a lesion is identified in a separate region (anterior region includes penis and scrotum and posterior region includes perineal and perianal region) or a lesion is identified with different morphology in the same region. For each biopsy, different instruments are to be used to prevent cross-contamination

between specimens. At the investigator's discretion, the lesion(s) may be surgically removed (therapeutic excision). In that case, the entire specimen must be submitted for analysis. All specimen(s) excised should be submitted to the central laboratory designated by the SPONSOR for analysis. For the genital wart/lesion biopsy, the external genital lesion biopsy kit provided by the SPONSOR central laboratory is to be used. Slides of the wart/lesion biopsy will be reviewed by a pathologist for the purpose of management of the subject. Management of anogenital warts is a study procedure, but the decision regarding the modality of therapy will be left to the discretion of the investigator, per the site's standard and practices. Excision of the wart/lesion is the preferred study treatment. All excised tissue is to be submitted to the central laboratory for analysis. If more than one biopsy is performed, then use separate instruments for each biopsy. Each biopsy should be placed in individual formalin containers. Treatment of anogenital warts by topical medications or cryotherapy is an acceptable study procedure. A biopsy of the identified lesion/lesions (e.g., morphology differs among identified lesions or more than one lesion is identified) must be obtained prior to administering treatment.

- The investigator should provide a clinical impression of the lesion, which should include one of the following: condyloma acuminata, other HPV-related lesion (e.g., Bowenoid papulosis, Bowen's disease), or other non-HPV related lesions.

- The location and anatomical area of each biopsied lesion should be identified and noted (as per the lab kit requisition supplied by the SPONSOR and should also be recorded in EDC system).

- To perform the biopsy, cleanse the biopsy area first with an antiseptic solution.

- Using a 25-30 gauge needle and a syringe containing 0.5 to 1 mL of 1% lidocaine or lidocaine with epinephrine, infiltrate below the epidermis of the wart. Optionally, a topical anesthetic cream may be applied over the biopsy site prior to infiltration with lidocaine to decrease the pain associated with needle insertion.

- Remove the wart tangentially with fine (iris) scissors or a scalpel blade to obtain the specimen.

- A different set of instruments is to be used for each biopsy taken.

- To promote hemostasis, apply gentle pressure. Styptic may be used. For larger areas, a single interrupted suture may be used. Electrocauterization is to be avoided, but the decision is left to the discretion of the practitioner. Silver nitrate is to be avoided, as it is reported to be more caustic and painful to the subject.

- Apply topical antibiotic ointment to the area to promote healing (optional).

- Management of anogenital warts will be left to the discretion of the investigator. Excision of the wart is an acceptable study treatment. All excised tissue is to be submitted to the central laboratory for analysis.

During genital wart treatment, follow-up biopsies should be obtained if new HPV-related lesions of differing morphology, and/or differing location appear. A recurrence is defined as the reappearance within 2 months of a lesion of similar morphology in the same anatomical location after complete resolution of the initial lesion. Recurring lesions will not be biopsied. Otherwise, all new lesions will be biopsied. The external genital lesion biopsies will be processed and read by a central laboratory chosen by the SPONSOR. These specimens will be processed at the central laboratory using study-specific guidelines. The central laboratory diagnosis will be used for management of subjects. However, this diagnosis will not be the diagnosis of record in the study. Rather all routine slides generated by the central laboratory will be sent to the Pathology Panel. The consensus diagnosis of this panel will represent the final diagnosis for study purposes. If the diagnosis of the Pathology Panel is worse than the diagnosis of central laboratory, then the investigator will be notified of the discrepancy in diagnoses.

External genital lesion specimens will also be used for HPV analysis. HPV analysis will be performed on Thinsection microtomy specimens. Each biopsy specimen will be analyzed by HPV PCR, regardless of whether an HPV-related histologic diagnosis is made, for the purpose of determining the causal HPV type in the lesion. Thinsection microtomy biopsy specimens will be tested for detection of HPV types 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59. In addition to this testing, specimens may be tested for other HPV types. HPV type 6, 11, 16 and 18 will be analyzed by type-specific multiplex (L1, E6 and E7 gene detection) PCR assay.

If a subject has an external genital lesion biopsy taken, that subject may remain in the study.

7.1.3.4 Serum for Anti-HPV Measurements

The 4-valent HPV cLIA is the primary assay used for the secondary objective 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 (non-heprinized, non-serum separator, redo-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 site should ship Retention serum separately from the Serum sample.

7.1.3.5 STI Testing

Local laboratory testing for Sexually Transmitted Infection (STIs) including chlamydia, gonorrhea, herpes simplex virus (HSV), syphilis, hepatitis B and HIV may be performed at any visit at the discretion of the investigator if clinically indicated. Abnormal results should be captured as new medical history at the next visit. In addition, per the exclusion criteria for this trial, known HIV-Positive subjects should not be enrolled in the trial.

7.1.3.6 Future Biomedical Research

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

- Blood for genomics use

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the next scheduled 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. If a subject must discontinue/withdraw after the Month 7 study visit, the subject should be asked to return for a final visit if it has been at least 4 months since the last trial visit. This visit would consist of the same specimen collections and tests conducted at the next scheduled visit and the subject would be formally discontinued from the study at the end of this visit. The discontinuation visit should not be done if it is medically contraindicated or if the subject refuses. If no discontinuation visit is performed, the subject should be formally discontinued from the study on the day the decision to discontinue is made. All attempts must be made to contact a subject who is lost to follow-up (a certified letter must be sent at the final attempt). Subjects who are lost to follow-up should be formally discontinued from the study on the day of the last unsuccessful attempt at contact.

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 writing to 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 PPD, 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

Disclosure envelopes containing vaccine/placebo disclosure information are stored and managed strictly and securely by the "MSD Emergency Center." The envelope should be opened only in the case of an emergency.

Envelopes are unsealed according to the following procedures.

When the investigator or sub-investigator needs to identify the clinical material received by a subject in case of emergency, e.g., the occurrence of serious adverse experiences, he/she will contact "MSD Emergency Center" by telephone and make a request for emergency key unblinding. As requested by the investigator or sub-investigator, "MSD Emergency Center" will provide the information to him/her promptly and report the Disclosure envelopes unblinding to the Sponsor. "MSD Emergency Center" will make a record promptly. However, the investigator or sub-investigator must enter the intensity of the adverse experiences observed, their relation to study drug, the reason thereof, etc. in the medical chart, etc. before unblinding the emergency key in principle. After the unblinding of the study, disclosure envelopes are to be returned to the Sponsor.

7.1.4.3 Specimens Taken Outside the Context of the Study

Tissue biopsies collected outside the context of the study are strongly discouraged. "Outside the context of the study" is defined as processing of samples at a local laboratory rather than through the SPONSOR-designated Central Laboratory. If a subject undergoes a biopsy outside the context of the study, all efforts will be made to obtain the operative report, local pathology report, diagnostic slides (for tissue biopsies), tissue block for slide preparation, PCR analysis and pathology panel review.

7.1.4.4 Subject Relocation

Given the duration of the study and the age of the study population, it can be expected that subjects may relocate during the study. The SPONSOR must be contacted for each temporary and permanent relocation as soon as the situation is known. Every effort should be made to adjust study visits around a subject's temporary absence (e.g., college breaks, summer vacation) so that the visits will be within the visit windows.

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:

1) 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.
2) The subject has not received any systemic (oral or parenteral) corticosteroids in the 2 weeks prior to any study vaccination visit.
3) 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.

7.1.5.2 Prerequisites for Study Visits with Specimen Collection

See the inclusion/exclusion criteria for specific restrictions at Visit 1 (Day 1). For visits that include collection of study specimens, study personnel should verify by questioning the subject that the subject has refrained from sexual activity (vaginal and anal penetration and any genital contact) for 2 calendar days prior to any visit that includes collection of swabs, and/or biopsies specimens.

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 the course of the use of the Sponsor's product in clinical trials or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Adverse events may also occur in screened subjects during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

All adverse events will be collected from the time the consent form is signed 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, and such events will be recorded at each examination on the Adverse Event case report forms/worksheets.

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

Administration of more 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 serious adverse event, even if no other seriousness 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 Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information can be found in the Investigator Trial File Binder.

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 a cancer;
- Is associated with an overdose;
- Is an other important medical event

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

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause, that occurs to any subject from the time the consent is signed 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, whether or not related to the Sponsor's product, must be reported within 24 hours to the

Sponsor either by electronic media or paper. Sponsor Contact information can be found in the Investigator Trial File Binder.

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 resulted in the subject discontinuing the trial

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.

7.2.2.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information can be found in the Investigator Trial File Binder.

Events of clinical interest for this trial include:

- an overdose of Sponsor's product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

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 4 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 [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); or	
	†Is a congenital anomaly/birth defect (in offspring of subject taking the product regardless of time to diagnosis); or	
	Is a cancer; or	
	Is associated with an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	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 U.S. CLINICAL MONITOR 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 there is another obvious cause of the AE. (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.

7.3 TRIAL GOVERNANCE AND OVERSIGHT

7.3.1 Data Monitoring Committee

To supplement the routine trial monitoring outlined in this protocol, an external Data Monitoring Committee (DMC) will monitor the interim data from this trial. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the trial in any other way (e.g., they cannot be trial investigators) and must have no competing interests that could affect their roles with respect to the trial. The DMC will include 2 clinicians experienced in urology/dermatology and 1 external statistician; this is in addition to the unblinded trial statistician who will be a non-voting member of the committee.

The DMC will make recommendations to the Sponsor regarding steps to ensure both subject safety and the continued ethical integrity of the trial. The DMC will review interim trial results, consider the overall risk and benefit to trial participants (see Section 8.1.5 - Interim Analyses) and recommend to the Sponsor if the trial should continue in accordance with the protocol.

Specific details regarding responsibilities and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the trial governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is reviewed and approved by the DMC. The DMC will monitor the trial at an appropriate frequency, as described in the detailed DMC charter. The DMC will also make recommendations to the Sponsor protocol team regarding steps to ensure both subject safety and the continued ethical integrity of the trial.

A DMC recommendation will be communicated to the Sponsor as agreed to in the Collaboration agreement based on reviewing the interim analysis results.

7.3.2 Clinical Adjudication Committee

The HPV Vaccine Program Pathology Panel will be responsible for providing the definitive pathologic diagnoses of external genital lesion biopsies for study purpose (not for medical management). Slides from external genital lesion biopsies will be evaluated by HPV Vaccine Program Pathology Panel. The HPV Vaccine Pathology Panel will prepare reports on each tissue specimen without knowing the vaccination groups of subjects. A separate guideline that details the HPV Vaccine Program Pathology Panel process has been approved by the HPV Program Pathology Panel.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

This section contains a brief summary of the statistical analyses for this trial. Full detail is in the Statistical Analysis Plan (SAP) (Section 8.2).

8.1.1 Efficacy Analyses

The efficacy endpoints, analysis population, and statistical methods to be employed for the efficacy analyses are presented in Table 3. The Per-Protocol Efficacy population will consist of subjects who receive the full vaccination series within 1 year, and have 1 or more follow-up visits following Month 7, do not have any general protocol violations, and are seronegative at baseline and PCR-negative from baseline through Month 7 for the relevant HPV type.

Table 3 Summary of Analysis Strategy for Efficacy Endpoint

Endpoint/Variable (Description)	Statistical Method	Analysis Population	Missing Data Approach
Primary Objective			
HPV6/11/16/18 related persistent infection	Exact 95% CI for vaccine efficacy	PPE	Not imputed
PPE=Per-Protocol Efficacy. HPV=human papilliomavins. CI=Confidence Interval			

The study is case-driven and the final analysis will be conducted at the time of 18 persistent infection cases collected, if no early stop for efficacy in interim analysis which is planned to be conducted at the time of 11 cases collected.

8.1.2 Safety Analyses

All subjects who received at least 1 study vaccination and have follow-up data will be included in the analysis of safety. The primary interest for safety will be the incidence of vaccine-related serious adverse experiences, which will be summarized and tabulated.

8.1.3 Immunogenicity Analyses

Anti-HPV6, 11, 16, 18 seroconversion percentages and Geometric Mean Titer (GMT) by Month 7 will be evaluated by computing point estimates and constructing 95% Confidence Intervals (CI) for all subjects, and for HM and MSM subjects, respectively.

8.1.4 Power and Sample Size

This study will enroll approximately 1100 subjects. For Asian males in Protocol V501-020, the observed incidence rate for HPV6/11/16/18-related Persistent Infection among placebo recipients was 2.3 per 100 person-years with the vaccine efficacy of 100%. If the true incidence rate on HPV6/11/16/18-related Persistent Infection is 2.3 per 100 person-years in Japanese males, with the assumption of vaccine efficacy of 85%, about 59% of enrolled subjects with evaluable data and one interim analysis at time of 11 persistent infection cases collected, the study will have at least 90% power to achieve success for the primary hypothesis. With the assumption of vaccine efficacy of 90%, the study will have more than 98% power to achieve success for the primary hypothesis. The total number of persistent

infection cases needed to keep the power is 18. The statistical criterion for success requires that the lower bound of the two-sided 95% confidence interval for vaccine efficacy be greater than 0. The rate of drop-out is estimated as 0.41 based on Protocol V501-020. The details are as follows: no general protocol violation: 95%; exclusion rate due to Day1 seropositive or PCR positive between Day 1 and Month 7 to HPV 6, 11, 16, and 18 is not greater than 15%; 90% of randomized subjects completed vaccination phase and 80% of Month 7 subjects complete 30-month follow-up period.

8.1.5 Interim Analysis

There is one planned interim analysis in this trial. The interim analysis will occur after 11 persistent infection cases are collected. The trial has >56% power to detect significant vaccine efficacy at alpha=0.006 one-sided in interim analysis if the true vaccine efficacy is 85%. A p-value of 0.6% for vaccine efficacy approximately corresponds to equal or less than 1 of 11 persistent infection cases occurring in the vaccine group.

8.2 Statistical Analysis Plan

There are no plans to issue a separate Statistical Analysis Plan (SAP) for this trial. If, after the trial has begun, important changes are made that affect principal features of the primary or key secondary analyses, then the protocol will be amended, as appropriate (consistent with ICH Guideline E-9). Any other changes made to the planned analyses after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR) for the trial. Post hoc exploratory analyses will be clearly identified in the CSR.

8.2.1 Responsibility for Analyses

The statistical analysis of the data obtained from this trial will be the responsibility of the Clinical Biostatistics department of the SPONSOR.

This study will be conducted as a double-blind study under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, protocol violators have been identified, and data have been declared final and complete.

8.2.2 Trial Objectives

See Section 3.0 for primary objectives.

8.2.3 Analysis Endpoints

8.2.3.1 Efficacy Endpoints

(1) Primary Endpoint: the incidence of HPV 6-, 11-, 16- or 18-related persistent infection.

Persistent infection is defined to have occurred if any of the following occurs:

- The subject is positive by an HPV PCR assay (type 6, 11, 16, or 18) to at least 1 common gene for the given vaccine HPV type in 2 consecutive anogenital or biopsy samples collected at least 4 months apart; OR

- The subject has Pathology Panel consensus diagnosis of condyloma acuminata, PIN, penile, perianal or perineal cancer AND detection of HPV 6, 11, 16 or 18 by Thinsection PCR in an adjacent section of the same biopsy block AND is PCR positive for the same HPV type to at least 1 common gene in the sample obtained at a separate adjacent visit, prior to or following the biopsy showing HPV disease.

(2) Secondary Endpoint: combined incidence of HPV 6-, 11-, 16- or 18-related persistent infection, condyloma acuminata, PIN, penile, perianal or perineal cancer.

Disease is defined to have occurred if on a single biopsy or excised tissue, there is

- Pathology Panel consensus diagnosis of condyloma acuminata, penile/perianal/perineal intraepithelial neoplasia (PIN), penile, perianal or perineal cancer; AND

- At least one of HPV types 6, 11, 16, or 18 is detected by Thinsection PCR in an adjacent section from the same tissue block.

(3) Exploratory Endpoint: combined incidence of HPV 6-, 11-, 16- or 18-related condyloma acuminata

8.2.3.2 Immunogenicity Endpoints

The immunogenicity endpoints are seroconversion percentages by Month 7 to each of HPV 6, 11, 16, and 18. Seroconversion is defined as changing serostatus from seronegative to seropositive. A subject with a cLIA titer at or above the serostatus cutoff for a given HPV type is considered seropositive for that type. The immunogenicity endpoint includes cLIA GMTs at each time point. On total IgG, same exploratory analysis will be conduct.

8.2.3.3 Safety Endpoints

Safety assessment will focus on the injection site adverse experiences/vaccine-related adverse experiences prompted for on the VRC occurring Day 1 through Day 5 following any vaccination, elevated temperature from Day 1 to 5 following any vaccination and systemic adverse experiences/vaccine-related adverse experiences occurring Day 1 through Day 15 following any vaccination. Serious adverse experiences occurring Day 1 through Day 15 following any vaccination, serious vaccine-related adverse experiences and new medical condition occurring any time during the study will be summarized.

8.2.4 Analysis Populations

8.2.4.1 Efficacy Analysis Population

Three subject populations will be considered for the efficacy analyses: 1 per-protocol population and 2 modified intention-to-treat (MITT) populations. The efficacy analysis using the per-protocol population will be the primary analysis for the primary and the secondary endpoints related to HPV types 6, 11, 16 and 18. Supplemental analyses for those endpoints will be provided using the 2 MITT populations. The per-protocol and MITT populations differ with regard to the inclusion/exclusion of protocol violators who are described below.

Per-Protocol Efficacy (PPE) Populations

To be included in the per-protocol analyses, subjects must:

(1) Have received all 3 vaccinations with the correct dose of the correct clinical material within 1 year, and have 1 or more follow-up visits following Month 7,

(2) Be seronegative to the appropriate HPV type(s) at baseline and PCR-negative to the appropriate HPV type(s) on all swabs and biopsies from baseline through Month 7,

(3) Have a Month 7 visit within a day range considered acceptable (14 to 72 days following the Month 6 vaccination) for defining the subject's Month 7 PCR status,

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

(5) Subjects must have refrained from sexual intercourse for 2 days prior to the visit at which infection or detection is determined.

(6) Not receive any nonstudy inactivated vaccine within 14 days before or after a study vaccination, or any nonstudy live virus vaccine within 28 days before or 14 days after a study vaccination;

(7) Not receive any immune globulin or blood-derived products at any time through Month 7 of the study;

The final determination on protocol violations, which will be used for determining the PPE population, will be made prior to the database lock and will be documented in a separate memo.

To be included in the effectiveness analysis with respect to either HPV type 6 or 11, subjects must be negative at the aforementioned time points for both HPV 6 and 11. For evaluations of efficacy with respect to any other vaccine HPV type, subjects need only be negative at the aforementioned time points for the HPV type under evaluation.

Full analysis set (FAS)

The populations will be restricted to subjects who received at least 1 vaccination and have any follow-up visit. General protocol violators will be included. All efficacy cases occurring after Day 1 will be counted. The population will not be restricted to subjects who are seronegative and PCR-negative at Day 1 to the appropriate HPV types. Subjects who receive incorrect clinical material or an incorrect dose of vaccine will be included in the analysis in the group to which they were randomized.

Modified Intention-to-Treat (MITT) Population

The populations will be restricted to subjects who received at least 1 vaccination and have any follow-up visit. General protocol violators will be included. All efficacy cases occurring after Day 1 will be counted. The MITT population (also labeled as HNRT [Naïve to the Relevant HPV type]) will include only subjects who are seronegative and PCR-negative at Day 1 to the appropriate HPV types. In the MITT population, subjects who receive incorrect clinical material or an incorrect dose of vaccine will be included in the analysis in the group to which they were randomized.

8.2.4.2 Immunogenicity Analysis Populations

The primary analysis population will be the Per-Protocol Immunogenicity (PPI) population. To be included in this population, subjects must satisfy all the criteria for the PPE population, and additionally must:

(1) have received all vaccinations within acceptable day ranges (see Table 4)
(2) have provided blood samples for serology testing within the acceptable day range (see Table 5)

A supportive analysis of immunogenicity will be conducted on the All Naïve Subjects With Serology (ANSS) population. To be included in this population, subjects must have received at least one dose of study vaccine, must have provided serology data, and must have been seronegative at Day 1 and PCR-negative from Day 1 through Month 7 to the appropriate HPV types. Subjects who receive incorrect clinical material or an incorrect dose of vaccine will be included in the analysis in the group to which they were randomized. Immune responses at 4 weeks postdose 3 will also be summarized in subjects who are (1) seropositive and PCR negative at Day 1; (2) seronegative and PCR positive at Day 1; and (3) seropositive and PCR positive at Day 1, for the given HPV type.

Table 4 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 5 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 36	Serum	1095	913 to 1277

† 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.

8.2.4.3 Safety Analysis Population

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

8.2.5 Statistical Methods

8.2.5.1 Statistical Methods for Efficacy Analyses

There are two efficacy analyses planned in this study. At the time when 11 cases of persistent HPV 6-, 11-, 16- or 18-related infection have been observed in the PPE population, an interim analysis will be conducted. If non-significant results are reached in the interim analysis, the final analysis will occur at the time of 18 cases of persistent HPV 6-, 11-, 16- or 18-related infection observed. The study conclusions regarding the vaccine efficacy will be made based on these analyses.

The primary efficacy hypothesis for vaccine efficacy >0% against persistent infection will be tested based on the number of cases among vaccine recipients relative to the total number of cases. A one-sided exact test based on a binomial distribution which conditions on the total number of cases will be used. The vaccine efficacy is defined $(1 - R_{V501} / R_{placebo}) * 100$ [%], where R_{V501} and $R_{placebo}$ are persistent infection incidence for V501 and placebo. The 95% confidence interval for the vaccine efficacy is calculated based on a proportion (p) of V501 recipients among all cases. The exact 95% confidence interval for p is calculated based on F distribution, and the exact 95% confidence interval for vaccine efficacy can be computed from the confidence bounds for p. The estimate of vaccine efficacy is adjusted by the "ratio of the amount of follow-up" (k), where k = (total amount of follow-up in the placebo group / total amount of follow-up in the V501 group). The relationship between p and the vaccine efficacy is as follows.

The point estimate of the vaccine efficacy ($\hat{\pi}$) = [1- p (1 + k)] / (1- p)

The 95% lower confidence limit for the vaccine efficacy = [1- pu (1 + k)] / (1- pu)

The 95% upper confidence limit for the vaccine efficacy = [1- pl (1 + k)] / (1- pl)

Where pu and pl are the upper and lower bounds of the exact confidence interval for p respectively.

Secondary efficacy endpoint and exploratory endpoint will be analyzed via the same manner used for the primary efficacy analysis.

Table 6 summarizes the efficacy analyses to be performed, and they are described in detail in the following sections.

Table 6 Efficacy Endpoints, Statistical Methods and Analysis Populations

Endpoint	Statistical Method	Analysis Population
Primary Endpoint: HPV6/11/16/18 related persistent infection		
Tests of Efficacy Hypotheses		
HPV 6/11/16/18 related persistent infection	Analysis of VE†	PPE
Supplementary Efficacy Analyses		
Overall and by HPV Type	Analysis of VE	PPE, HNRT, FAS
Impact of Baseline Characteristics		
Age, Sexual Orientation, Circumcision, Smoking, Lifetime Sexual Partners, Presence of Other HPV Types	Analysis of VE	PPE
Robustness of Persistent Infection Definition		
Persistent infection relaxing the 6 month (+/- 1 month) interval requirement (i.e., ≥ 0 months duration)	Analysis of VE	PPE
Persistent infection requiring 2, 3, or 4consecutive positive results over ≥ 12 months duration	Analysis of VE	PPE
Robustness of DNA Detection Definition		
Incident DNA Detection at 1 or More Visits	Analysis of VE	PPE
Secondary Endpoint: HPV6/11/16/18 related persistent infection, condyloma acuminata, PIN, and penile/ perianal/ perineal cancer		
Tests of Efficacy Hypotheses		
HPV 6/11/16/18 related persistent infection and disease	Analysis of VE	PPE
Supplementary Efficacy Analyses		
Overall, by HPV Type, by Persistent Infection or Disease, by Lesion type	Analysis of VE	PPE, HNRT, FAS
Impact of Baseline Characteristics		
Age, Sexual Orientation, Circumcision, Smoking, Lifetime Sexual Partners, Presence of Other HPV Types	Analysis of VE	PPE
Other Endpoint		
Intra-anal persistent infection		
HPV 6/11/16/18-Related Intra-anal Persistent Infection – Overall, by HPV Type	Analysis of VE	PPE, HNRT, FAS
HPV 6/11/16/18-Related Intra-anal Persistent Infection – Overall, by Baseline Characteristics (Age, Sexual Orientation, Circumcision, Smoking, Lifetime Sexual Partners, Presence of Other HPV Types)	Analysis of VE	PPE
Persistent infection excluding intra-anal persistent infection		
HPV 6/11/16/18-Related Persistent Infection excluding Intra-anal Persistent Infection – Overall, by HPV Type	Analysis of VE	PPE, HNRT, FAS
HPV 6/11/16/18-Related Persistent Infection excluding Intra-anal Persistent Infection – Overall, by Baseline Characteristics (Age, Sexual Orientation, Circumcision, Smoking, Lifetime Sexual Partners, Presence of Other HPV Types)	Analysis of VE	PPE
Time to Event Analysis		
Time to Occurrence of HPV 6/11/16/18-Related persistent infection	Kaplan-Meier Estimate	PPE, HNRT, FAS
Time to Occurrence of HPV 6/11/16/18-Related persistent infection and diseases	Kaplan-Meier Estimate	PPE, HNRT, FAS
Time to Occurrence of HPV 6/11/16/18-Related intra-anal persistent infection	Kaplan-Meier Estimate	PPE, HNRT, FAS
Time to Occurrence of HPV 6/11/16/18-Related persistent infection excluding intra-anal persistent infection	Kaplan-Meier Estimate	PPE, HNRT, FAS
Therapeutic Efficacy	Analysis of VE	Day 1 PCR- and Sero+
HPV 6/11/16/18-Related Persistent Infection – Overall, by HPV Type	Analysis of VE	Day 1 PCR- and Sero+
HPV 6/11/16/18-Related Intra-anal Persistent Infection – Overall, by HPV Type		
HPV 6/11/16/18-Related Persistent Infection excluding intra-anal persistent infection – Overall, by HPV Type	Analysis of VE	Day 1 PCR- and Sero+
Incidence of clearance of HPV 6/11/16/18 Infection	Estimation of Incidence‡	Day 1 PCR+ and Sero-, Day 1 PCR+ and Sero+

† refers to point and confidence interval estimation of vaccine efficacy (1-relative risk)
‡ refers to point and confidence interval estimation of incidence, expressed as rate per 100 person-years
HPV = Human Papillomavirus; VE = Vaccine Efficacy; PIN = Penile/Perianal/perineal intraepithelial neoplasia;
PPE = Per-protocol efficacy; FAS = Full analysis set; HNRT = Naïve to the Relevant HPV type;
PCR = Polymerase chain reaction; PCR+ = PCR positive; PCR- = PCR negative; Sero+ = Seropositive; Sero- = Seronegative

Computation of Follow-Up Time
Follow-up for the primary analysis begins following the Month 7 visit. Therefore the follow-up time for a subject will be the interval in days between his Month 7 visit and his last day of follow-up. For cases, this will be the visit at which the biopsy detecting the endpoint was taken. If a subject develops more than one case of disease that fits into a given endpoint classification, the final visit date will be the date at which the first of these endpoints was detected. For non-cases, the last day of follow-up will be defined as the cutoff date when the database is locked for analysis. Follow-up time will be similarly calculated for secondary and exploratory endpoints.

For the MITT analyses, follow-up begins following Day 1 instead of Month 7, so the follow-up time for a subject will be the interval in days between the Day 1 visit and the last day of follow-up, as described above.

The date of occurrence of each endpoint is defined as follows. For disease cases, it is the date of the sample from which the diagnosis of disease was made. For persistent infection it is the date of the first consecutive sample which was positive for HPV by PCR.

Kaplan-Meier estimates of the time-to-event curves will be generated for certain efficacy endpoints. Subjects without the endpoint will be censored at the end of their follow-up time, as defined in this section.

8.2.5.2 Statistical Methods for Immunogenicity Analyses

There are no formal immunogenicity hypotheses comparing the vaccination groups since it is anticipated that placebo recipients will have anti-HPV titers below the limit of detection of the cLIA and total IgG assay.

Estimation of seroconversion percentage
The seroconversion percentages with respect to anti-HPV 6, 11, 16, 18, by Month 7 will be evaluated by computing point estimates and constructing 95% CI. Calculation of the CI is based on the exact binomial method proposed by Clopper and Pearson (1934).

Estimation of GMTs
Anti-HPV 6, 11, 16, 18 GMT at Month 7 will be evaluated by computing point estimates and constructing 95% CI. The values will be log transformed before analysis. As such, the CI 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 CI will yield estimates for the population GMT and CI about the GMT on the original scale.

Persistence of immune responses
Anti-HPV 6, 11, 16, 18 GMTs and seroconversion percentages at Months 7 and 36 will be summarized in the PPI population to assess the persistence of immune responses. Longitudinal plots of the GMTs from Day 1 through Month 36 will also be provided for graphical display.

8.2.5.3 Statistical Methods for Safety Analyses

All subjects who received at least one injection and have follow-up data will be included in the analysis of safety, including protocol violators and subjects discontinuing from the study.
The following approach will be used for the analysis of safety parameters across all injections.
To provide an overall assessment, summary measures such as the incidence of (a) any adverse experiences; (b) any injection-site experiences; (c) any systemic adverse experiences; and (d) any vaccine-related adverse experiences will be summarized in both groups. Adverse experiences will be summarized as frequencies and percentages by vaccination group, by vaccination visit and across all vaccination visits. To address specific adverse experiences, the incidences of injection-site adverse experiences Days 1 to 5 and specific systemic adverse experiences within 14 days postvaccination occurring in at least 1% of the subjects will be tabulated. Risk differences between the vaccination groups will be estimated and their 95% two-sided confidence intervals calculated, by the method of Miettinen and Nurminen [33].

Statistical testing of no difference in safety parameters between the vaccine and placebo group will be restricted to injection site adverse experiences prompted for on the VRC (namely, injection site pain, redness and swelling), and for temperature elevations (maximum oral equivalent temperature ≥37.5°C), across all vaccination visits. The testing will use the method of Miettinen and Nurminen [33] for a difference in proportions.
Tables of specific adverse experiences will be restricted to those events occurring in at least 1% of either vaccination group. Tables will also be generated for the subsets of subjects who were seropositive to at least one of the vaccine HPV types at Day 1, and who were seronegative to all vaccine HPV types at Day 1.
The incidence of greatest adverse experience intensity (mild, moderate, severe) reported by a subject will be tabulated for: all injection site adverse experiences (Day 1 to Day 5 following any vaccination visit); all systemic adverse experiences (Day 1 to Day 14 following any vaccination visit); any adverse experience (Day 1 to Day 14 following any vaccination visit). For those injection site events which are measured (redness and swelling), 0 to 1 inch would be categorized as mild, >1 inch to 2 inches will be categorized as moderate and >2 inches will be categorized as severe. Similar tables will be produced summarizing the greatest intensity per subject for each of the prompted adverse experiences individually.

The distribution of maximum temperatures recorded from Day 1 to Day 5 following each injection on VRCs will be summarized. The proportions of subjects who experience a maximum temperature of at least 37.5°C (oral equivalent) across all vaccination visits and by visit, will be provided.

8.2.5.4 Subgroup Analyses and Effect of Baseline Factors

The impact of baseline characteristics on efficacy outcomes will be explored by presenting vaccine efficacy estimates within subsets defined by the characteristics listed in Section 8.2.5.1.
Data permitting, all the planned analysis will be provided both for HM and MSM subgroups.

8.2.6 Multiplicity

This study tests one primary endpoint which is performed at up to 2 analysis times (1 interim analysis and a final analysis).
The overall probability of making a false claim of superiority, across the two analysis times, is controlled at level 0.025. The nominal alpha levels for positive vaccine efficacy findings were 0.006 at interim analysis and 0.02273 at final analysis. One formal interim analysis for the primary endpoint will be conducted during the study. The gamma spending function, used for alpha on endpoints as outlined by Hwang, Shih, and DeCani [34] was used in calculation. The information time for the interim analyses will be based on the proportion of events observed during the study.

8.2.7 Sample Size and Power Calculations

This study will enroll approximately 1100 subjects. For Asian males in Protocol V501-020, the observed incidence rate for HPV6/11/16/18-related Persistent Infection among placebo recipients was 2.3 per 100 person-years with the vaccine efficacy of 100%. If the true incidence rate on HPV6/11/16/18-related Persistent Infection is 2.3 per 100 person-years in Japanese males, with the assumption of vaccine efficacy of 85%, about 59% of enrolled subjects with evaluable data and one interim analysis at time of 11 persistent infection cases observed, the study will have at least 90% power to achieve success for the primary hypothesis. The total persistent infection cases needed to keep the power is 18. With the assumption of vaccine efficacy of 90%, the study will have more than 98% power to achieve success for the primary hypothesis. The power for a given number of observed primary endpoints was computed using the method of Chan and Bohidar [35]. The statistical criterion for success requires that the lower bound of the two-sided 95% confidence interval for vaccine efficacy be greater than 0. The rate of drop-out is estimated as 0.41 based on V501 PN020 study. The details are as follows: no general protocol violation 95%; exclusion rate due to Day1 seropositive or PCR positive between Day 1 and Month 7 to HPV 6, 11, 16, and 18 is not greater than 15%; 90% of randomized subjects completed vaccination phase and 80% of Month 7 subjects completed 30-months' follow-up period.

8.2.8 Interim Analysis

One interim analysis will be performed in this study. Results will be reviewed by a DMC. The endpoint, timing, and purpose of the interim analysis are summarized in Table 7 below.

Table 7 Summary of Interim Analysis Strategy

Endpoint for interim Analysis	Timing of Interim Analysis	Purpose of Interim Analysis
HPV6/11/16/18 related persistent infection	11 persistent infection cases are documented across the 2 arms	Getting significant VE results earlier

The main purpose of the interim analysis s is to make a superiority claim earlier. The primary endpoint at interim analysis is to be tested with overall one-sided alpha = 0.006. The spending function preserves much of the alpha for the final analysis (alpha=0.02273). The exact method was used to calculate the actual alpha spending in interim analysis [35] and HSD method was used to decide the alpha for the final analysis [34]. If one or less persistent

infection case is observed in vaccine group among total 11 persistent infection cases, significant results can be reached. If the true vaccine efficacy is 85% we have 57% probability to make a superiority claim. With vaccine efficacy of 90%, the probability will increase to 73.6%

The decision rules are driven by the one-sided p-values and vaccine efficacy, Table 8 summaries the alpha spending and corresponding powers at interim analysis and final analysis. Interim analysis will be conducted by an unblinded statistician.

Table 8 Alpha Spending and Corresponding Powers at Interim Analysis and Final Analysis

Vaccine Efficacy	Interim analysis		Final Analysis		Overall Significant Probability
	Boundary p-values	Significant Probability	Boundary p-values	Significant Probability	
85%	0.006	57.0%	0.0227	83.1%	92.7%
90%	0.006	73.6%	0.0227	93.0%	98.1%

At Interim Analysis, the frequency of adverse experiences among vaccinated patients will also be evaluated in each vaccination group.

An independent DMC will carefully monitor the formal safety and efficacy interim results of this trial. In terms of efficacy, the DMC will use the guidelines proposed below for recommendation of either continuation or early termination of the study at the interim analysis. Additionally, the DMC will review safety data of the ongoing study at close, regular intervals as specified in the DMC charter. Such safety data will be summarized by blinded vaccination groups. A detailed description of the structure, function, and guidelines for decision-making by the DMC are also outlined in the DMC charter.

8.2.9 Compliance

Compliance is defined in this study as receipt of all scheduled study vaccinations. The numbers of subjects who receive each vaccination will be tabulated by vaccination group
The numbers of subjects who complete each follow-up visit will be tabulated by vaccination group. The numbers of subjects with biopsies or excision procedures performed outside of the study and the numbers of these subjects for whom the tissue samples were not available, will be tabulated by vaccination group. Differences in these numbers will be assessed observationally and the potential impact on the efficacy analyses noted.
Exposure to vaccine will be summarized by tabulating the number of subjects receiving each of the three study vaccinations.

8.2.10 Missing Data

There will be no imputation of results where data are missing. Biopsy samples with missing PCR results cannot be counted as a case for the primary analysis.

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 or matching Placebo	Sterile suspension for IM injection

9.2 Packaging and Labeling Information

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

Subjects will receive one (1) blinded vial of V501 or matching placebo at Day 1 (Visit 1), Month 2 (Visit 2) and Month 6 (Visit 3). No kitting is required.

9.3 Clinical Supplies Disclosure

Supplies will be provided with random code/disclosure envelopes or lists containing drug disclosure information. The Sponsor will provide one sealed envelope to the central emergency unblinding center for each randomization number.

Drug identification information is to be unmasked ONLY if necessary for the welfare of the subject. Every effort should be made not to unblind the subject unless necessary.

In the event that unblinding has occurred, the circumstances around the unblinding (e.g., date and reason) must be documented promptly, and the Sponsor Clinical Monitor notified as soon as possible. Only the principal investigator or delegate and the respective subject's code should be unblinded. Trial site personnel and Sponsor personnel directly associated with the conduct of the trial should not be unblinded.

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 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.

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 or through a secure password-protected electronic portal 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 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 discarding 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 by the Sponsor.

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

i. 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.

ii. 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.

iii. 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

1. 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.

2. 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.

3. 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.

4. 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

1. 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.

2. 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.

3. 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

1) 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]

2) Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug response.2

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

4) DNA: Deoxyribonucleic acid.

5) RNA: Ribonucleic acid.

2) Scope of Future Biomedical Research

The DNA specimen(s) collected in the current trial will be used to study various causes for how subjects may respond to a drug. The DNA specimen(s) will be stored to provide a resource for future trials conducted by Merck focused on the study of biomarkers responsible for how a drug enters and is removed by the body, how a drug works, other pathways a drug 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, 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 Merck or designees and research will be monitored and reviewed by a committee of our scientists and clinicians.

3) Summary of Procedures for Future Biomedical Research

- Subjects for Enrollment

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

- 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. Information contained on the consent form alone cannot be traced to any specimens, test results, or medical information once the specimens have been rendered de-identified.

Subjects are not required to participate in the Future Biomedical Research sub-trial in order to participate in the main trial. Subjects who decline to sign the Future Biomedical Research informed consent will not have the specimen collected nor will they be discontinued from the main trial.

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.

Each informed consent approved by an ethics committee is assigned a unique tracking number. The tracking number on this document will be used to assign specimen permissions for each specimen into the Entrusted Keyholder's Specimen Database.

- eCRF Documentation for Future Biomedical Research Specimens

  Documentation of both consent and acquisition of Future Biomedical Research specimens will be captured in the electronic Case Report Forms (eCRFs). Reconciliation of both forms will be performed to assure that only appropriately-consented specimens are used for this sub-trial's research purposes. Any specimens for which such an informed consent cannot be verified will be destroyed.

- Future Biomedical Research Specimen Collections

  Blood specimens for DNA or RNA isolation will usually be obtained at a time when the subject is having blood drawn for other trial purposes. Specimens like tissue and bone marrow will usually be obtained at a time when the subject is having such a procedure for clinical purposes.

  Specimens will be collected and sent to the laboratory designated for the trial where they will be processed (e.g., DNA or RNA extraction, etc) following the Merck approved policies and procedures for specimen handling and preparation.

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, Merck has developed secure policies and procedures. All specimens will be de-identified 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.

This first code will be replaced with a second code at a Merck designated storage/lab facility. The second code is linked to the first code via a second key. The specimen is

now double coded. Specimens with the second code are sometimes referred to as de-identified specimens. The use of the second code provides additional confidentiality and privacy protection for subjects over the use of a single code. Access to both keys would be needed to link any data or specimens back to the subject's identification.

The second code is stored separately from the first code and all associated personal specimen identifiers. A secure link, the second key, will be utilized to match the second code to the first code to allow clinical information collected during the course of the trial to be associated with the specimen. This second key will be transferred under secure procedures by the Merck designated facility to an Entrusted Keyholder at Merck. The second code will be logged into the primary biorepository database at Merck and, in this database, this identifier will not have identifying demographic data or identifying clinical information (i.e., race, sex, age, diagnosis, lab values) associated with it. The specimen will be stored in a designated biorepository site with secure policies and procedures for specimen storage and usage.

The second key can be utilized to reconstruct the link between the results of future biomedical research and the clinical information, at the time of analysis. This linkage would not be possible for the scientist conducting the analysis, but can only be done by the Merck Entrusted Keyholder under strict security policies and procedures. The Merck Entrusted Keyholder will link the information and then issue a de-identified data set for analysis. The only other circumstance by which future biomedical research data would be directly linked to the full clinical data set would be those situations mandated by regulatory authorities (e.g., EMEA, FDA), whereby this information would be directly transferred to the regulatory authority.

5) Biorepository Specimen Usage

Specimens obtained for the Merck Biorepository will be used for analyses using good scientific practices. However, exploratory analyses will not be conducted under the highly validated conditions usually associated with regulatory approval of diagnostics. The scope of research performed on these specimens is limited to the investigation of the variability in biomarkers that may correlate with a clinical phenotype in subjects.

Analyses utilizing the Future Biomedical Research specimens may be performed by Merck, or an additional third party (e.g., a university investigator) designated by Merck. The investigator conducting the analysis will be provided with double coded specimens. Re-association of analysis results with corresponding clinical data will only be conducted by the Merck Entrusted Keyholder. 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 the specific analysis is performed will be returned to the sponsor or destroyed and documentation of destruction will be reported to Merck.

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 writing to the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact Merck using the designated mailbox

PPD and a form will be provided by Merck 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 Merck 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 acquisition. 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 Merck 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 Merck policies and procedures and this destruction will be documented in the biorepository database.

8) Data Security

Separate databases for specimen information and for results from the Future Biomedical Research sub-trial will be maintained by Merck. This is done to separate the future exploratory test results (which include genetic data) from the clinical trial database thereby maintaining a separation of subject number and these results. The separate databases are accessible only to the authorized Sponsor 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 in international standards (e.g., ISO17799) to protect against unauthorized access. The Merck Entrusted Keyholder maintains control over access to all specimen data. These data are collected for future biomedical research purposes only as specified in this sub-trial will not be used for any other purpose.

9) Reporting of Future Biomedical Research Data to Subjects

There is no definitive requirement in either authoritative ethical guidelines or in relevant laws/regulations globally that research results have to be, in all circumstances, returned to the trial participant. Some guidelines advocate a proactive return of data in certain instances. No information obtained from exploratory laboratory studies will be reported to the subject or family, and this information will not be entered into the clinical database

maintained by Merck on subjects. Principle reasons not to inform or return results to the subject include: lack of relevance to subject health, limitations of predictive capability, concerns of misinterpretation and absence of good clinical practice standards in exploratory research typically used for diagnostic testing.

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 as to how to offer clinical diagnostic testing (paid for by Merck) to subjects enrolled and will be advised that counseling should be made available for all who choose to participate in this diagnostic testing.

If any exploratory results are definitively associated with clinical significance after completion of a clinical trial, Merck will publish the results without revealing specific subject information, inform all trial sites who participated in the Merck clinical trial and post anonymized results on our website or other accredited website(s) that allow for public access (e.g., disease societies who have primary interest in the results) in order that physicians and patients may pursue clinical diagnostic testing if they wish to do so.

10) Gender, Ethnicity and Minorities

Although many diagnoses differ in terms of frequency by ethnic population and gender, every effort will be made to recruit all subjects diagnosed and treated on Merck clinical trials for future biomedical research. When trials with specimens are conducted and subjects identified to serve as controls, every effort will be made to group specimens from subjects and controls to represent the ethnic and gender population representative of the disease under current investigation.

11) Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the subject have been minimized. [insert: 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.

Merck 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.

It is necessary for subject-related data (i.e., ethnicity, diagnosis, drug therapy and dosage, age, toxicities, etc.) to be re-associated to double coded specimens at the time of data analysis. These subject data will be kept in a separate, secure Merck database, and all specimens will be stripped of subject identifiers. No information concerning results obtained from future biomedical research will be entered into clinical records, nor will it be released to outside persons or agencies, in any way that could be tied to an individual subject.

12) Self-Reported Ethnicity

Subjects who participate in future biomedical research will be asked to provide self-reported ethnicity. Subjects who do not wish to provide this data may still participate in future biomedical research.

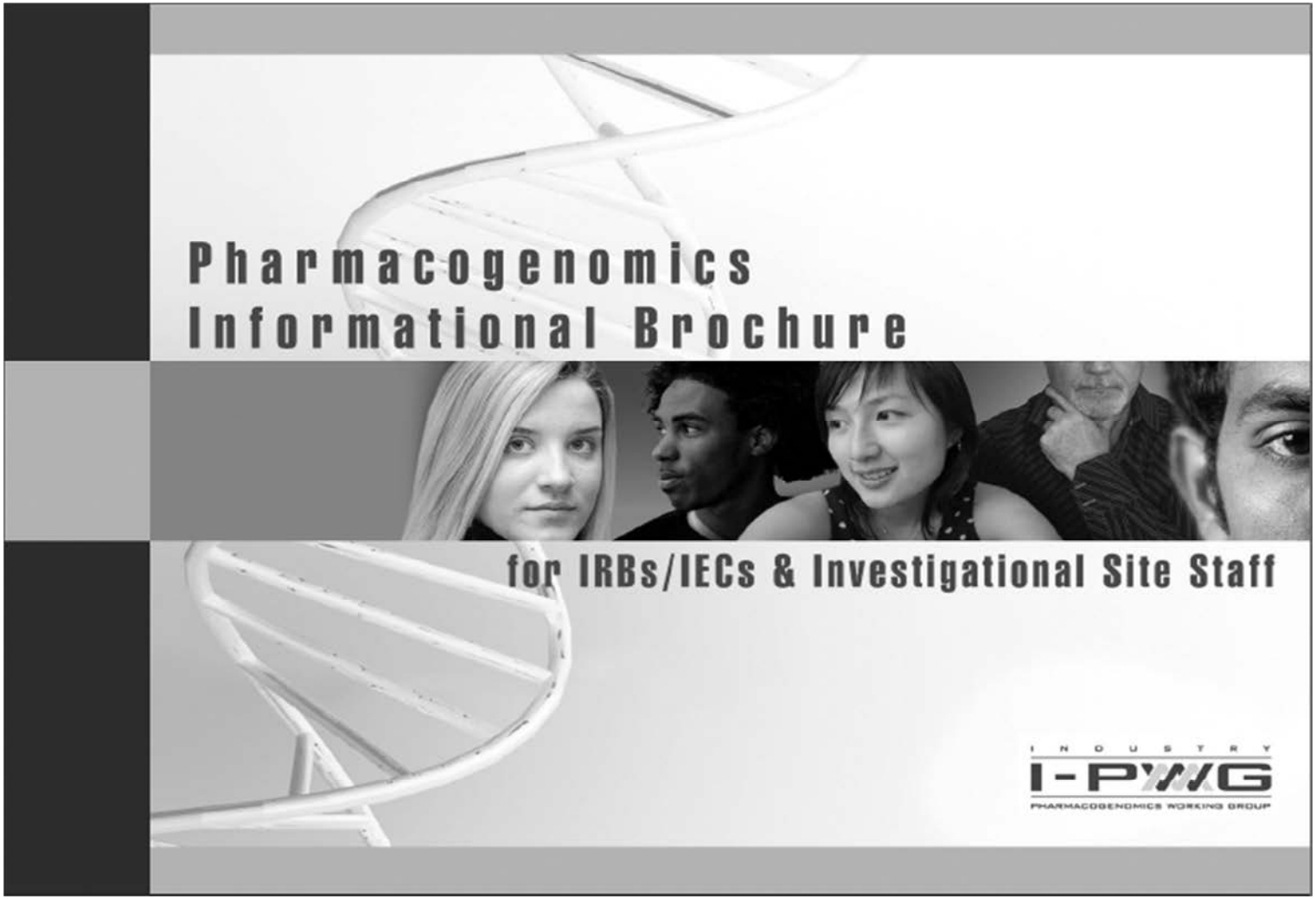
13) Questions

Any questions related to the future biomedical research should be e-mailed directly to PPD

14) References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker
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



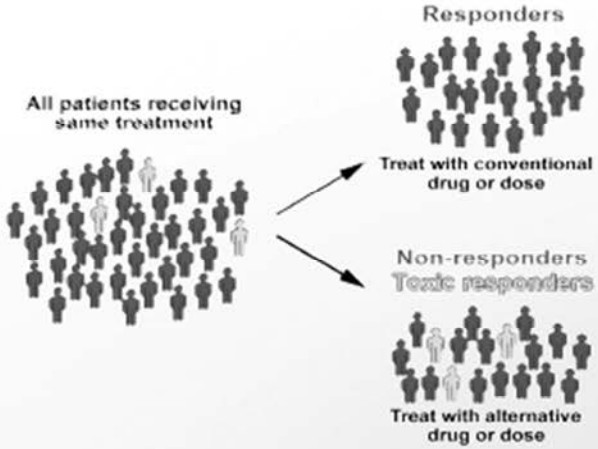
This Informational Brochure is intended for IRBs/IECs & Investigational Site Staff. The brochure was developed to address issues relevant to DNA collection and research in the context of pharmaceutical drug development.

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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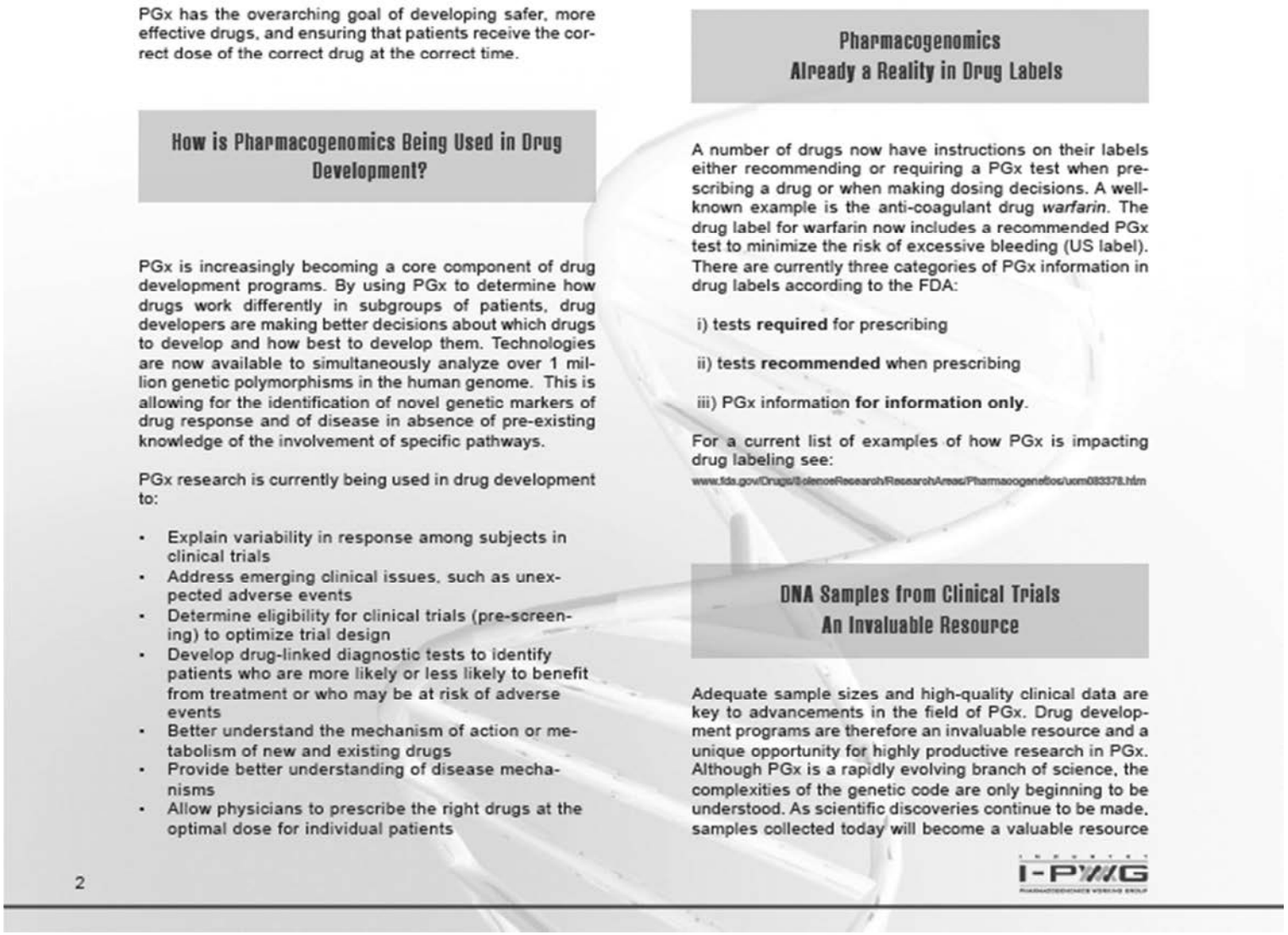

PGx has the overarching goal of developing safer, more effective drugs, and ensuring that patients receive the correct dose of the correct drug at the correct time.

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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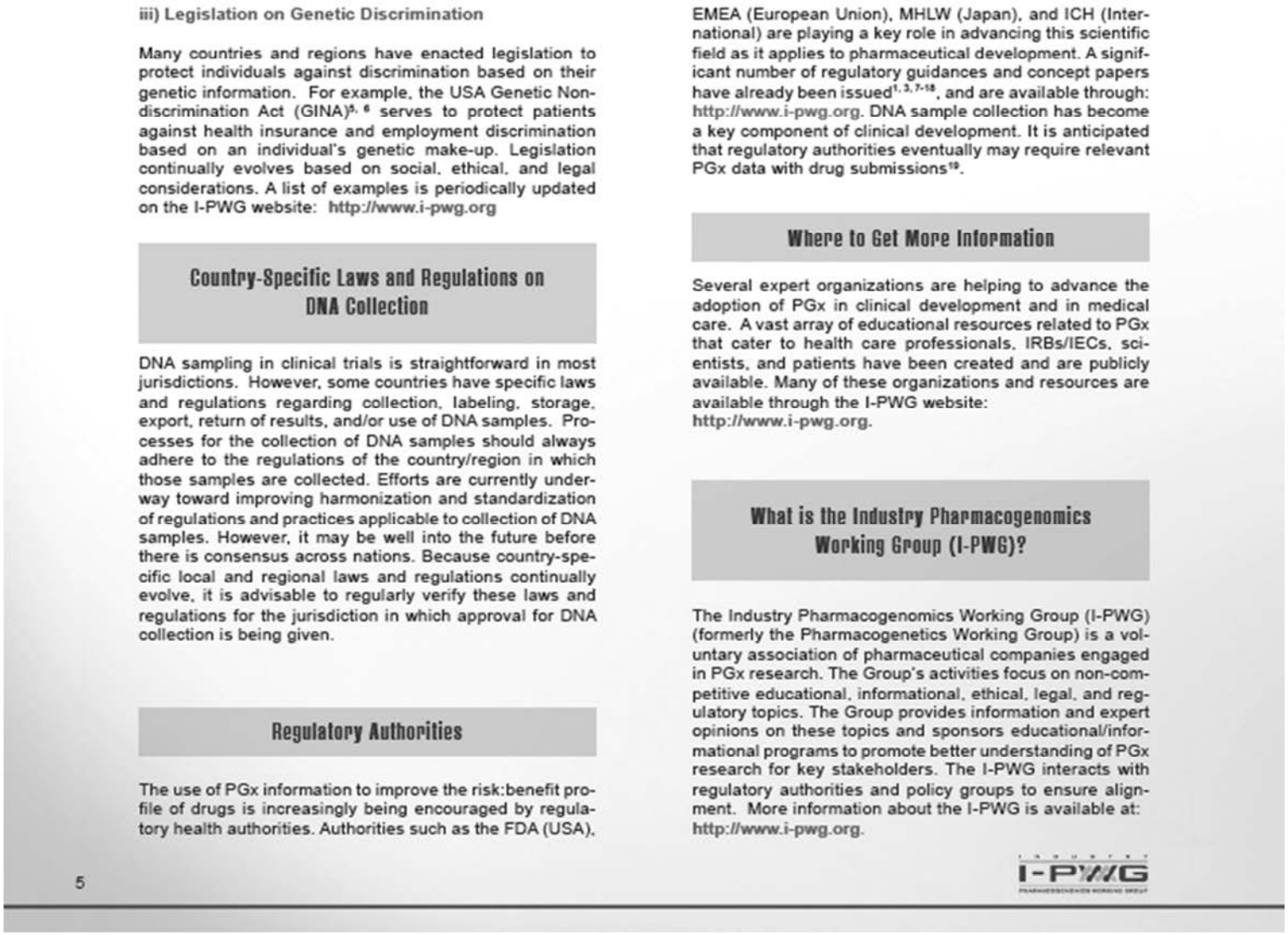

iii) Legislation on Genetic Discrimination

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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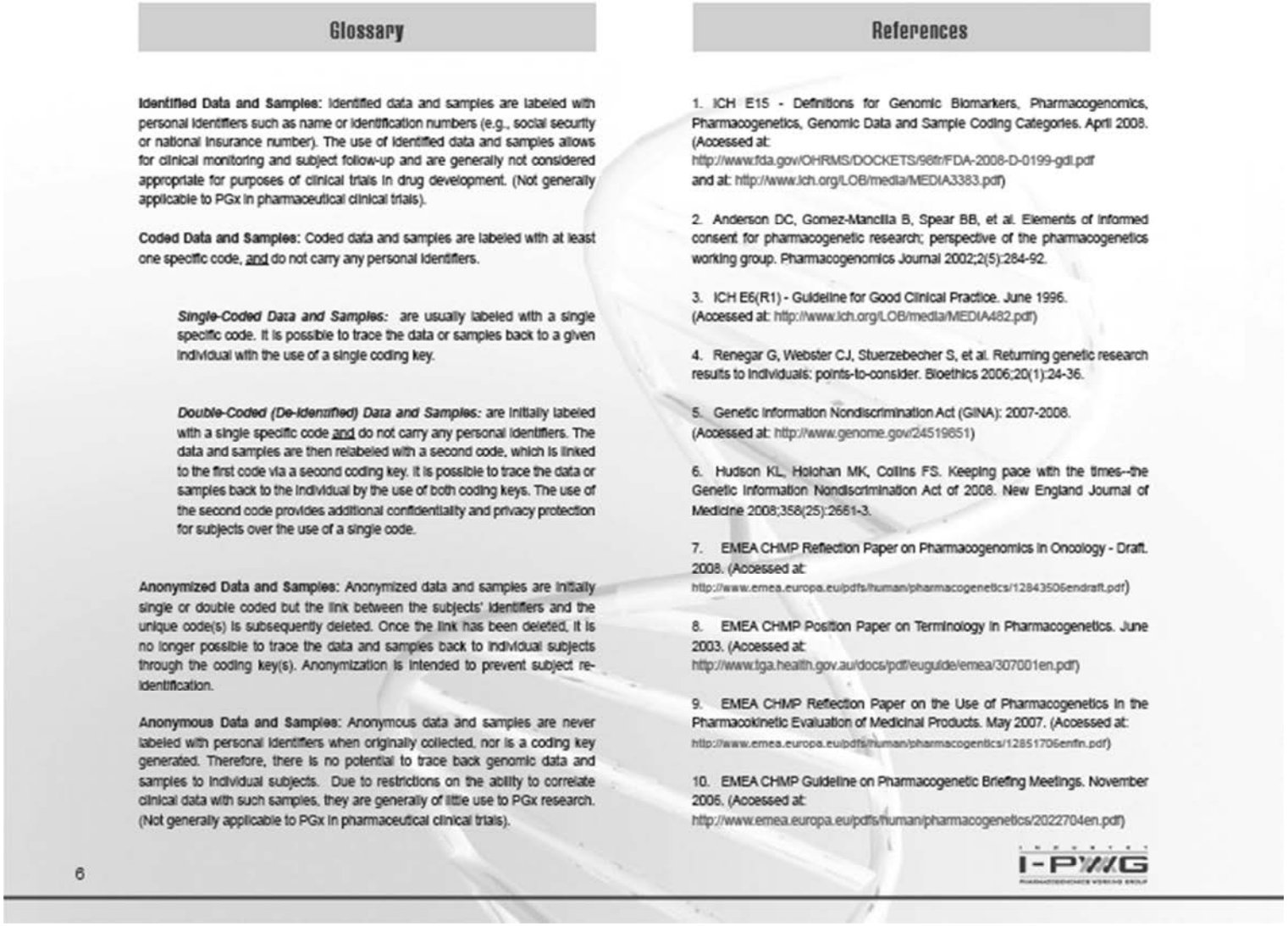
I-PWG



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).

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http://www.i-pwg.org

12.4 Clinical Study Conduct System

12.4.1 Sponsor

12.4.1.1 Name and Address of Sponsor

PPD

KITANOMARU SQURE 1-13-12, Kudankita, Chiyoda-ku, Tokyo 102-8667

12.4.1.2 Sponsor's Representative

PPD

PPD

Japan Development, MSD K.K.

KITANOMARU SQURE 1-13-12, Kudankita, Chiyoda-ku, Tokyo 102-8667

TEL: PPD FAX: PPD

Role of Sponsor's Representative

Sponsor's Responsible Medical Officer will sign the protocol as the representative of the Sponsor.

12.4.1.3 Medical Expert

PPD

PPD

Japan Development, MSD K.K.

KITANOMARU SQURE 1-13-12, Kudankita, Chiyoda-ku, Tokyo 102-8667

TEL: PPD FAX: PPD

12.4.1.4 Field Monitor (CRA) Representative

Site Monitoring, Japan Development, MSD K.K.

PPD

TEL: PPD FAX: PPD

12.4.2 Clinical Research Organizations

See Japanese version

12.4.3 Investigator

A list of the primary investigators and participating institutions is given in Attachment 1.

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	SIGNATURE	DATE
_____	_____	_____

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	SIGNATURE	DATE
_____	_____	_____