Official Protocol Title:	An Open-Label Phase III Clinical Trial to Study the Immunogenicity and Tolerability of GARDASIL®9 (A Multivalent Human Papillomavirus [HPV] L1 Virus-Like Particle [VLP] Vaccine) in Adult Women (27- to 45-Year-Olds) Compared to Young Adult Women (16 to 26 Year Olds)
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TITLE:

An Open-Label Phase III Clinical Trial to Study the Immunogenicity and Tolerability of GARDASIL®9 (A Multivalent Human Papillomavirus [HPV] L1 Virus-Like Particle [VLP] Vaccine) in Adult Women (27- to 45-Year-Olds) Compared to Young Adult Women (16 to 26 Year Olds)

EudraCT NUMBER: 2015-005093-38

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SUMMARY OF CHANGES

Primary Reason for this amendment

The primary reason for V503-004-02 protocol amendment is change in sponsor of this study from MSD Vaccins, a French société par actions simplifiée to Merck Sharp & Dohme Corp.,

Table 1 Protocol Amendment 2 - Summary of Changes

Section Number(s)	Section Title(s)	Description of Change(s)
NA	Title Page	Updated name and contact of the sponsor
2.2	Subject Inclusion Criteria	Updated inclusion criteria 5 to reflect standard text for the V503 program. Added instructions for contraceptive use for women with no childbearing potential.

ABBREVIATIONS AND DEFINITIONS

AE	adverse event
ANSS	all type-specific naïve subjects with serology
AW	adult women
cLIA	competitive Luminex® immunoassay
CRA	clinical research associate
e-CRF	electronic case report form
CSP	clinical study protocol
CSR	clinical study report
EDC	electronic data capture
EU	European Union
GMT	geometric mean titre
HPV	human papillomavirus
ICF	informed consent form
IEC	independent ethics committee
IMP	investigational medicinal product
IRT	Interactive response technology
mAbs	monoclonal antibodies
mMU/mL	milli merck units per millilitre
PPI	per protocol immunogenicity
qHPV	quadrivalent human papillomavirus vaccine
SAE	serious adverse event
VLP	virus-like particles
eVRC	Electronic vaccination report card
YAW	young adult women
9vHPV	9-valent (6/11/16/18/31/33/45/52/58) human papillomavirus vaccine

1.0 SUMMARY

1.1 Title

An Open-Label Phase III Clinical Trial to Study the Immunogenicity and Tolerability of GARDASIL®9 (A Multivalent Human Papillomavirus [HPV] L1 Virus-Like Particle [VLP] Vaccine) in Adult Women (27- to 45-Year-Olds) compared to Young Adult Women (16- to 26-Year-Olds)

1.2 Indication

Prevention of cervical, vulvar, vaginal, and anal cancers and related precancers, external genital lesions, Pap test abnormalities, and persistent infection caused by HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58.

1.3 Summary of Rationale

GARDASIL®9[1] is a prophylactic 9-valent human papillomavirus (9vHPV) (Types 6, 11, 16, 18, 31, 33, 45, 52, and 58) L1 virus-like particle (VLP) vaccine that is comprised of VLPs of the 4 human papillomavirus (HPV) types (Types 6, 11, 16, and 18) contained in GARDASIL®,[2] plus the VLPs of 5 additional oncogenic HPV types (Types 31, 33, 45, 52, and 58). This vaccine offers the potential of significant prophylactic cancer coverage in addition to that already provided by GARDASIL®, with an increase in overall cervical cancer coverage from approximately 70% to 90%.

GARDASIL®9 received marketing authorization in the European Union (EU) in June 2015 for active immunization of individuals from the age of 9 years against premalignant lesions and cervical, vulvar, vaginal and anal cancers caused by vaccine HPV types and genital warts (*Condyloma acuminata*) caused by specific HPV types.

The efficacy of GARDASIL® is relevant to GARDASIL®9 since the vaccines are manufactured by a similar process and contain 4 of the same HPV L1 VLPs.

As summarized in the GARDASIL®9 Summary of Product Characteristics, the efficacy of GARDASIL®9 was compared with that of the quadrivalent HPV (qHPV) vaccine with respect to HPV types 6, 11, 16, and 18. The population included girls and women between 16 to 26 years (Protocol 001) and girls between 9 to 15 years (Protocol 009). Immune responses for

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[1] GARDASIL®9 (Human Papillomavirus 9-valent Vaccine, Recombinant) is a registered trademark of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, New Jersey, U.S.A.

[2] GARDASIL [Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine] is a registered trademark of Merck & Co., Inc., Whitehouse Station, New Jersey, U.S.A. GARDASIL is also known as SILGARD in some countries. SILGARD is a trademark of Merck & Co., Inc., Whitehouse Station, New Jersey, U.S.A.

GARDASIL®9 were found to be non-inferior to immune responses for GARDASIL®. Of the subjects receiving GARDASIL®9, 99.6% to 100% became seropositive for antibodies against all 9 vaccine types by Month 7 across all groups tested. GARDASIL®9 was also found to be efficacious in preventing HPV 31-, 33-, 45-, 52-, and 58-related persistent infection and disease in girls and women between 16 to 26 years (Protocol 001).

Clinical study results suggest that women older than 26 years of age without evidence of prior exposure to the vaccine types can benefit from GARDASIL®.[3,4] The long-term effectiveness and safety of the GARDASIL® vaccine in older women have also been found to be high[5]. Studies also suggest that subjects who have been previously exposed to HPV might benefit from HPV vaccination.[6,7] In several EU countries such as Austria, Italy, Ireland, and Germany, there is acknowledgement of HPV vaccine benefit after HPV exposure and/or treatment. Canada and Australia have recommended the qHPV vaccine for women between 27 to 45 years of age.

Studies with GARDASIL®9 in women older than 26 years of age have not been conducted.

This study is designed to assess the safety and immunogenicity of GARDASIL®9 in 27- to 45-year-old women, to complete the evaluation of GARDASIL®9 in the extended age range of female subjects for whom GARDASIL® was proven to be effective. This study is primarily powered to demonstrate the non-inferior immunogenicity of GARDASIL®9 in 27- to 45-year-old women, compared with 16- to 26-year-old women, the population in which GARDASIL®9 has been demonstrated to be effective, with respect to the 7 oncogenic HPV types (Types 16, 18, 31, 33, 45, 52, and 58).

1.4 Summary of Study Design

This study will enrol a total of approximately 1,200 subjects, i.e., 600 women 16- to 26-years-old and 600 women 27- to 45-years-old, all of whom have not yet received a prophylactic HPV

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[3] Muñoz N, Manalastas R Jr, Pitisuttithum P, Tresukosol D, Monsonego J, Ault K, et al. Safety, immunogenicity, and efficacy of quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine in women aged 24–45 years: a randomised, double-blind trial. Lancet. 2009 Jun 6;373:1949-57.

[4] Castellsagué X, Muñoz N, Pitisuttithum P, Ferris D, Monsonego J, Ault K, et al. End-of-study safety, immunogenicity, and efficacy of quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine in adult women 24–45 years of age. Br J Cancer. 2011;105(1):28-37.

[5] Luna J, Plata M, Gonzalez M, Correa A, Maldonado I, Nossa C, et al. Long-term follow-up observation of the safety, immunogenicity, and effectiveness of Gardasil™ in adult women. PLoS ONE. 2013;8(12):e83431.

[6] Joura EA, Garland SM, Paavonen J, Ferris DG, Perez G, Ault KA, et al. Effect of the human papillomavirus (HPV) quadrivalent vaccine in a subgroup of women with cervical and vulvar disease: retrospective pooled analysis of trial data. BMJ. 2012 Mar 27;344:e1401.

[7] Kang WD, Choi HS, Kim SM. Is vaccination with quadrivalent HPV vaccine after loop electrosurgical excision procedure effective in preventing recurrence in patients with high-grade cervical intraepithelial neoplasia (CIN2-3)? Gynecol Oncol. 2013 Aug;130(2):264-8.

vaccine. The study will provide a comparison of immunogenicity of GARDASIL®9 in 27- to 45-year-old women, with 16- to 26-year-old women, with respect to the 7 oncogenic HPV types (Types 16, 18, 31, 33, 45, 52, and 58). The responses to the two non-oncogenic HPV types included in the vaccine (Types 6 and 11) will be presented using descriptive statistics. The number of subjects to be enrolled in the study was determined based on the primary immunogenicity objective.

All subjects will be administered a standard 3-dose regimen (Day 1, Month 2, Month 6) of GARDASIL®9. Serum samples will be collected on Day 1 and Month 7 for anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 antibody assays. The time point for comparison of immune responses will be Month 7, or approximately 4 weeks after the administration of the third dose. The safety/tolerability profile of the vaccine will be evaluated in all subjects in the study. Safety information will be collected on Day 1 through 1 month following the third vaccination or for a total of approximately 7 months for each subject.

The end of the study will be defined as when final report of study results is available.

1.5 Sample

This study will enrol healthy women in 2 age groups: 16- to 26-year-olds and 27- to 45-year-olds. Each age group will be further stratified into subgroups of 16- to 20-year-olds and 21- to 26-year-olds for young adult women (YAW) and 27- to 36-year-olds and 37- to 45-year-olds for adult women (AW). Enrolment will be monitored to make sure that no single age stratum (i.e., subgroup) exceeds 55% of the total sample of a given age group (i.e., enrolment in an age stratum will be stopped when around 330 subjects in that age stratum have been vaccinated).

1.6 Dosage/Dosage Form, Route, and Dose Regimen

Subjects will receive GARDASIL®9 (HPV 9-valent vaccine [recombinant, adsorbed]) administered as a 0.5-mL intramuscular injection on Day 1, Month 2 and Month 6. The vaccine formulation is summarized in Table 2.

GARDASIL®9 is available as a suspension for injection. It appears as a clear liquid with white precipitate.

Table 2 Vaccine Formulation (0.5-mL Dose)

HPV 6 (mcg)	HPV 11 (mcg)	HPV 16 (mcg)	HPV 18 (mcg)	HPV 31 (mcg)	HPV 33 (mcg)	HPV 45 (mcg)	HPV 52 (mcg)	HPV 58 (mcg)	Total VLP (mcg)	AAHS† (mcg)
30	40	60	40	20	20	20	20	20	270	500

† AAHS, Merck Aluminum Adjuvant (amorphous aluminum hydroxyphosphate sulfate)
HPV, human papillomavirus; VLP, virus-like particle.

1.7 Study Flow Chart

Visit Windows (a):	Consent Visit	2 months after Day 1, ±3 weeks	6 months after Day 1, ±4 weeks	3 to 7 weeks after Month 6
Event/Test	**Day 1 (Visit 1)**	**Month 2 (Visit 2)**	**Month 6 (Visit 3)**	**Month 7 (Visit 4) (b)**
Obtain informed consent form / assent	+			
Informed Consent for Future Biomedical Research	+			
Assign screening number	+			
Review inclusion/Exclusion criteria (c)	+			
Collect medical history (past year)	+			
Collect demographics	+			
Collect height and weight	+			
Update Medical History (new conditions not already recorded as medical history or adverse events (AEs)		+	+	+
Review medications and non-study vaccines (d)	+	+	+	+
Pregnancy test (serum or urine) (e)	+	+	+	+
Blood sample for anti-HPV antibody testing (including retention serum) (10 ml of blood each time) (f)	+			+
Blood (DNA) for Future Biomedical Research (j)	+			
Collect oral temperature (g)	+	+	+	

Visit Windows (a):	Consent Visit	2 months after Day 1, ±3 weeks	6 months after Day 1, ±4 weeks	3 to 7 weeks after Month 6
Event/Test	**Day 1 (Visit 1)**	**Month 2 (Visit 2)**	**Month 6 (Visit 3)**	**Month 7 (Visit 4) (b)**
Assign allocation number	+			
Perform vaccination (Intramuscular; prefer deltoid muscle of non-dominant arm; do not give in buttocks)	+	+	+	
Provide electronic vaccination report card (eVRC)	+			
Review and collect eVRC data (h)		+	+	+
Review AEs, clinical follow-up for safety (i)	+	+	+	+

(a) To calculate visit windows, assume 1 month equals 30 days and 1 week equals 7 days.
(b) Whenever possible, when a subject discontinues/withdraws prior to study completion, all applicable activities scheduled for the final study visit should be performed at the time of discontinuation except for serum collection for HPV testing.
(c) A physical examination may be performed during Visit 1 if deemed necessary by the investigator to assess eligibility criteria.
(d) See Section 3.2.2.2 for details of documentation times and time period restrictions for medications and non-study vaccines. If other non-study vaccines are administered at any time during the study, they should not be administered in the same limb as the study vaccine and must be appropriately documented.
(e) The serum or urine pregnancy test will be performed per the manufacturer's instructions. A pregnancy test will be performed before administration of each dose of the study vaccine and at the final Month 7 visit on all subjects. The pregnancy test must be performed prior to serum collection for HPV testing at Day 1.
(f) Blood sample for anti-HPV measurements must be collected prior to the first study vaccination. Serum must be shipped as specified by the Sponsor. The retention serum vial must remain at the study site until the Sponsor notifies the study site to ship the samples. Leftover main study serum sample will be stored for future biomedical research if the subject consents to the Future Biomedical Research.
(g) If the subject has a fever (defined as an oral temperature of ≥37.8°C or 100.0°F) 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. Oral temperature will be measured prior to each vaccination
(h) The investigator should instruct the subject to use the eVRC to document oral temperature in the evening after each study vaccination and daily, at the same time of day, for 4 days after each study vaccination. Additionally, injection-site and systemic adverse event(s) (AEs), concomitant medications, and concomitant vaccinations are to be documented in the eVRC starting after each study vaccination for a total of 15 days, including the day of vaccination (Day 1 to Day 15).
(i) Observe subjects for at least 15 minutes after each vaccination for immediate untoward effects. Serious adverse events (SAEs), pregnancy events, and lactation events should be reported to the Sponsor's , within 24 hours. Adverse events and SAEs will be followed for 15 days and 30 days, respectively, after the last dose (i.e., after the third dose for subjects completing the vaccination schedule or after the last received dose in the event of the subject withdrawing).
(j) Informed consent for future biomedical research samples must be obtained to collect the DNA sample.

2.0 CORE PROTOCOL

2.1 Objectives and Hypotheses

2.1.1 Primary Objective

To demonstrate that the administration of GARDASIL®9 in 27- to 45-year-old women induces non-inferior geometric mean titres (GMTs) for serum anti-HPV 16, 18, 31, 33, 45, 52, and 58 compared with 16- to 26-year-old women.

Hypothesis: GARDASIL®9 induces in 27- to 45-year-old women anti-HPV 16, 18, 31, 33, 45, 52, and 58 GMTs at 4 weeks after Dose 3 that are non-inferior to those induced in 16- to 26-year-old women who are seronegative at Day 1 to the relevant HPV types. (The GMT ratios for HPV 16, 18, 31, 33, 45, 52, and 58 will be analysed separately. The statistical criterion for non-inferiority requires the lower bound of the two-sided 95% confidence interval (CI) of the GMT ratio [27- to 45-year-old women versus 16- to 26-year-old women] to be greater than 0.50 for each HPV type).

2.1.2 Secondary Objectives

The secondary objectives are:

To evaluate the safety/tolerability of GARDASIL®9 in 27- to 45-year-old women compared with 16- to 26-year-old women;

To demonstrate that GARDASIL®9 is immunogenic with respect to HPV types 16, 18, 31, 33, 45, 52, and 58 in 27- to 45-year-old women;

To summarize humoral immune responses (including anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 GMTs and seroconversion rates at Day 1 and 4 weeks after Dose 3) in 16- to 26-year-old and 27- to 45-year-old women who received GARDASIL®9.

Hypothesis: GARDASIL®9 generates anti-HPV 16, 18, 31, 33, 45, 52 and 58 seroconversion rates 4 weeks after Dose 3 that are acceptable in 27- to 45-year-old women who are seronegative at Day 1 to the relevant HPV type(s). (Seroconversion is defined as changing serostatus from seronegative at Day 1 to seropositive by 4 weeks after Dose 3) (The seroconversion rate for each of the HPV types 16, 18, 31, 33, 45, 52, and 58 will be tested separately. Acceptability is defined as the lower bound of the two-sided 95% CI for the seroconversion rate being greater than 90%).

2.2 Subject Inclusion Criteria

To be included in the study and to receive the first study vaccination, subjects must meet all inclusion criteria. For items with an asterisk (*), if the subject does not meet these inclusion criteria, the Day 1 visit may be rescheduled for a time when these criteria can be met.

1. Independent Ethics Committee (IEC)-approved written informed consent form (ICF) and privacy language as per national regulations must be obtained from the subject and/or

from the subject's parent(s) or legal guardian(s) prior to any study-related procedures (including discontinuation of prohibited medication, if applicable); assent (for minor subjects) by the subject is given as required by local law. The subject may also provide consent/assent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.

2. Subject is a woman between the ages 16 years and 0 days and 45 years and 364 days as of first vaccination.
3. Subject is judged to be in good physical health on the basis of medical history, physical examination (if deemed necessary), and laboratory testing.
4. Subject, or subject's parent or guardian, is able to understand and adhere to the study procedures (e.g., is not planning to relocate far from the investigational centre during the study period); is able to read, understand, and complete the electronic vaccination report card (eVRC); is able to understand the risks involved with the study; and voluntarily agrees to participate in the study by giving written informed consent.
5. *Since the first day of the subject's last menstrual period through Day 1, the subject has not had sex with males or has had sex with males and used effective contraception with no failures (an example of a failure is a male condom that ruptures during sexual intercourse). Effective contraception is defined as a marketed, approved contraceptive product that the subject has used per the manufacturer's instructions with every act of sexual intercourse. The subject understands and agrees that during the Day 1 through Month 7 period, she should not have sexual intercourse with males without effective contraception, and the uses of the rhythm method alone, withdrawal alone, and emergency contraception, are not acceptable methods per the protocol. Subjects who have reached menopause, undergone hysterectomy, bilateral oophorectomy, or bilateral tubal ligation are eligible without the use of contraceptives. Postmenopausal status is defined as: (1) No menses for >1 year but <3 years and confirmed by follicle stimulating hormone (FSH) levels elevated into the postmenopausal range, or (2) no menses for at least 3 years.
6. * Subject has had no temperature ≥37.8°C or 100.0°F (oral) within 24 hours prior to the first injection.
7. Subject agrees to provide study personnel with a primary telephone number as well as an alternate telephone number for follow-up purposes.

2.3 Subject Exclusion Criteria

To be included and receive the first study vaccination, subjects should not have any exclusion criteria. For items with an asterisk (*), if the subject meets these exclusion criteria, the Day 1 visit may be rescheduled for a time when these criteria are not met.

1. Subject has a history of an abnormal Pap test or abnormal cervical biopsy results (showing cervical intraepithelial neoplasia or worse) or cervical disease (i.e., surgical treatment for cervical lesions).

2. Subject has history of genital warts, Vulvar Intraepithelial Neoplasia or Vaginal Intraepithelial Neoplasia.
3. Subject has a history of a positive test for HPV.
4. Subject has a history of known prior vaccination with an HPV vaccine, i.e., received a marketed HPV vaccine, or has participated in an HPV vaccine clinical study and has received either active agent or placebo.
5. Subject is pregnant (as determined by serum or urine pregnancy test).
6. Subject is, at the time of signing ICF, a user of recreational or illicit drugs or has had a recent history (within the last year) of drug or alcohol abuse or dependence. Alcohol abusers are defined as those who drink despite recurrent social, interpersonal, and/or legal problems as a result of alcohol use.
7. Subject has a history of severe allergic reaction, including known allergy to any vaccine component, including aluminum, yeast, or BENZONASE® (nuclease, Nycomed [used to remove residual nucleic acids from this and other vaccines]) (e.g., swelling of the mouth and throat, difficulty breathing, hypotension or shock) that met the criteria for serious adverse experiences defined in this protocol.
8. Subject has had a splenectomy, or is currently immunocompromised or has been diagnosed as having a congenital or acquired immunodeficiency, HIV infection, lymphoma, leukaemia, systemic lupus erythematosus, rheumatoid arthritis, juvenile rheumatoid arthritis, inflammatory bowel disease, or other autoimmune or immunosuppressive condition, or has a history of any disease, which, in the investigator's opinion, may confound the results of the study or pose an additional risk to the subject.
9. Subject is receiving or has received in the year prior to enrolment the following immunosuppressive therapies: radiation therapy, cyclophosphamide, azathioprine, methotrexate, any chemotherapy, cyclosporin, leflunomide (tumour necrosis factor-α antagonists, monoclonal antibody therapies (including rituximab [Rituxan]), 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 she is currently receiving steroid therapy, has recently (defined as within 2 weeks of enrolment) received such therapy, or has received 2 or more courses of high dose corticosteroids (≥20mg/day of prednisone [or equivalent] orally or parenterally) lasting at least 1 week in duration in the year prior to enrolment. Subjects using inhaled, nasal, or topical corticosteroids are considered eligible for the study.
10. Subject has received any immune globulin or blood-derived product within the 3 months prior to the Day 1 vaccination, or plans to receive any such product during Day 1 through Month 7 of the study.
11. * Subject has received non-replicating (inactivated) vaccines within 14 days prior to the Day 1 vaccination or has received replicating (live) vaccines within 21 days prior to the Day 1 vaccination.

12. Subject has thrombocytopenia or other coagulation disorder that would contraindicate intramuscular injections.
13. Subject is concurrently enrolled in a clinical study of investigational agent.
14. Subject 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.
15. Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or Sponsor staff directly involved with this trial.

2.4 Study Design and Duration

2.4.1 Summary of Study Design

This is an international, multicentre; open-label, immunogenicity and tolerability study of GARDASIL®9 in 16- to 45-year-old women.

Approximately 1,200 healthy women, all of whom have not yet received a prophylactic HPV vaccine, will be enrolled in the study (i.e., 600 YAW between 16 to 26 years of age and 600 AW between 27 to 45 years of age). Each age group will be divided in 2 strata defined as 16- to 20-year-olds and 21- to 26-year-olds for YAW and 27- to 36-year-olds and 37- to 45-year-olds for AW. The immunogenicity data will be summarized by strata and age group, and the safety data will be summarized for 16- to 26-year-old women and 27- to 45-year-old women. All enrolled subjects will receive a 3-dose regimen (Day 1, Month 2, and Month 6) of GARDASIL®9. Serum samples will be obtained on Day 1 and Month 7 for anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 testing. Immunogenicity analyses will be performed after all subjects have completed the Month 7 visit.

Medical history (past year) will be collected on Day 1 for all subjects. Oral temperature will be measured prior to each vaccination. Vital signs (height, weight, and oral temperature) will be collected on Day 1. Physical examination will be conducted on Day 1 if deemed necessary by the investigator.

Subjects will be monitored for safety and tolerability from Day 1 through 1 month following the third vaccination or for a total of approximately 7 months for each subject. A pregnancy test will be performed before administration of each dose of the study vaccine and at the final Month 7 visit on all subjects. The pregnancy test must be performed prior to serum collection for HPV testing at Day 1. Any subject with a positive pregnancy test at Day 1 will not be vaccinated and will not be allowed to participate in the study. Subjects with a positive pregnancy test after Day 1 will not be vaccinated with subsequent doses until resolution of the pregnancy as outlined in Table 3. Pregnant subjects who receive less than 3 vaccinations during the study will be offered the possibility to complete the vaccination course. Pregnancies and associated adverse experiences will be followed to outcome.

2.4.2 Treatment Plan

Approximately 1,200 healthy women will receive GARDASIL®9 as a 3-dose regimen of 0.5-mL intramuscular injections administered on Day 1, Month 2, and Month 6.

Study vaccine must be stored in a refrigerator that has a temperature between 2 °C and 8°C (35.6°F and 46.4°F). If the refrigerator in which the study vaccine is stored deviates from the 2°C to 8°C (35.6°F and 46.4°F) range, study vaccinations should be suspended and the Sponsor or designee should be contacted immediately so that an investigation can be conducted.

2.5 List of Immunogenicity Measurements

Serum will be collected for analysis of anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 responses by competitive Luminex® immunoassay (cLIA). Serum will be analysed to support the primary and secondary objectives.

At Day 1, blood samples will be collected prior to the first study vaccination to identify subjects who have been exposed to study vaccine HPV types prior to enrolment. Serology results at Day 1 are not part of the inclusion/exclusion criteria; thus, no subject will be excluded from the study based on these results. After Day 1, serum specimens will be collected at the Month 7 study visit as specified in the Study Flow Chart (Section 1.7).

2.6 List of Safety Measurements

Each subject will receive an electronic VRC at the Day 1, Month 2, and Month 6 study vaccination visits. On the eVRC, the subject or the subject's parent or guardian will be asked to record oral temperature in the evening after each study vaccination and daily, at the same time of the day, for 4 days after each vaccination for the purpose of identifying febrile events. In addition, beginning after each study vaccination and for a total of 15 days including the day of vaccination (Day 1 to Day 15), the subject will be asked to record injection-site and systemic adverse events (AEs), concomitant medications, and concomitant vaccinations on the eVRC.

Serious adverse events (SAEs), pregnancy information, and lactation information will also be collected as described in Section 3.4. In addition, new medical conditions not present at baseline and not reported as an AE (i.e., incident medical conditions occurring outside of a Day 1 to Day 15 period post-vaccination and not considered SAEs) will be collected throughout the study. In case of pregnancy, the pregnancy and any serious adverse experiences in study subjects and their infants must be followed to outcome. In addition, if subjects receive study vaccine while breastfeeding during the Day 1 through Month 7 period, any serious adverse experiences in the study subjects and their infants must be followed to outcome.

2.7 Data Analysis Summary

2.7.1 Immunogenicity Analyses

The primary analyses of immunogenicity will be conducted in the Per Protocol Immunogenicity (PPI) population as defined in Section 3.5.4.1.

The primary hypotheses of non-inferiority of GMTs for HPV oncogenic types 16, 18, 31, 33, 45, 52, and 58 will be based on one-sided tests of non-inferiority comparing Month 7 GMTs for each component. Analysis of variance (ANOVA) models (one per HPV oncogenic type) with a response of log individual titres and a fixed effect for age group will be used. The hypotheses to be tested are: H_0: $GMT_{AW}/GMT_{YAW} \leq 0.50$ versus H_1: $GMT_{AW}/GMT_{YAW} > 0.50$, where GMT_{AW} represents the GMTs in 27- to 45-year-old subjects and GMT_{YAW} represents the GMTs in 16- to 26-year-old subjects. Each hypothesis will be tested at $\alpha=0.025$ level (one-sided). The statistical criterion for non-inferiority in these tests corresponds to the lower bound of the two-sided 95% CI for the geometrical mean ratio of 27- to 45-year-old subjects versus 16- to 26-year-old subjects being greater than 0.50. Success of the study will be declared if non-inferiority can be confirmed for all HPV oncogenic types. Therefore, no adjustment for multiplicity is required.

For this study on women 16- to 45-years of age, the rate of exclusion from the PPI analysis populations is expected to range from 25% to 35% of enrolled subjects mainly due to HPV seropositivity at baseline and possibly protocol deviations that could potentially interfere with immune response to vaccination of GARDASIL®9. The expected GMT ratio AW/YAW is 0.7, reflecting the fact that the immunogenicity of any HPV vaccine decreases with the increasing age of the subjects, and the variability (standard deviation) of each serotype on the natural log scale is estimated to be 1.2. If 1,200 subjects are enrolled in the study in a 1:1 fashion with regards to the 2 age groups, the evaluable population will range from 780 to 900 subjects. If the exclusion rate from PPI analysis population is 35% for 1 HPV type and 25% for the 6 others, this study will have over 90% power to rule out a 2-fold decrease in GMT for the 7 oncogenic HPV types (Types 16, 18, 31, 33, 45, 52, and 58).

The secondary hypotheses of acceptability of the anti-HPV 16, 18, 31, 33, 45, 52 and 58 seroconversion rates in the 27- to 45-year-old women group will be tested based on the 95% CIs for the single group proportion calculated using the exact binomial method (Clopper-Pearson method) for single proportions. For each HPV type, the statistical criterion for acceptability requires that the lower bound of the 95% CIs of the seroconversion rate for each of the antigens is greater than 90%.

Assuming a true seroconversion rate to each HPV type >98% and a percentage of subjects excluded from the PPI analysis population <35% for HPV 16 and <25% for HPV 18, 31, 33, 45, 52 and 58, the power of the secondary hypothesis testing is >99% using a Type I error $\alpha=0.025$ (one-sided).

Another secondary objective is to summarize HPV antibody responses (including anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 GMTs and seroconversion rates at Day 1 and 4 weeks after Dose 3) in 16- to 26-year-old and 27- to 45-year-old women who received GARDASIL®9. In

addition, exploratory analyses will be conducted to provide HPV antibody responses by age strata (i.e., 16- to 20-year-olds and 21- to 26-year-olds for YAW and 27- to 36-year-olds and 37- to 45-year-olds for AW).

2.7.2 Safety Analyses

All subjects who received at least 1 dose of GARDASIL®9 and have safety follow-up data will be included in the analysis of safety. Statistical analyses of AEs will follow the 3-tiered analysis approach commonly used by the Sponsor/Vaccine Manufacturer when conducting safety assessments.

Tier 1 analysis compares between group difference by providing incidence summaries by each group, computing (incidence) risk differences and 95% CIs of risk differences between groups and computing p-values corresponding to tests of significance of the risk differences. P-values and 95% CIs for between-age-group differences in the percentage of subjects with events will be calculated using the Miettinen and Nurminen [20] method.

Tier-1 AEs in this study include:

- injection-site adverse reactions prompted for on the eVRC occurring Day 1 to Day 5 following any vaccination, and
- elevated temperatures (≥37.8°C or 100.0°F) from Day 1 to Day 5 following any vaccination.

Tier 2 analysis follows the Tier 1 analysis approach, except p-values are not computed.

Tier-2 AE summaries include:

- systemic AEs within 14 days following any vaccination occurring in ≥1% of subjects in any group,
- injection-site adverse reactions not prompted for on the eVRC occurring Day 1 to Day 5 following any vaccination in ≥1% of subjects in any group,
- SAEs occurring within 14 days (Day 1 to Day 15) following any vaccination,
- serious vaccine-related AEs observed at any time during the study, and
- severe injection-site adverse reactions Day 1 to Day 5 following any vaccination visit.

Tier-3 AEs include summaries (counts and percentages) by each age-group for any other AEs, including all injection-site adverse reactions occurring from Day 1 to Day 5 following each vaccination visit, all systemic AEs occurring within 14 days (Day 1 to Day 15) of each vaccination visit, and all SAEs occurring during the study and not included in the Tier-2 analysis.

2.8 DATA MONITORING COMMITTEE

Since its market introduction in 2006, over 183 million doses of GARDASIL® have been distributed (as of April 2015). The safety profile is well characterized and continuously monitored by routine post-marketing surveillance activities. Based on the continued medical monitoring performed by the 9vHPV vaccine (V503) clinical team, its overall safety profile appears to be similar to that of GARDASIL® [22].

In June 2015, GARDASIL®9 (V503) was granted marketing authorization in Europe. Since this is an open-label Phase 3 study, a Data Monitoring Committee was not deemed necessary in this context.

3.0 PROTOCOL DETAILS

3.1 Rationale

3.1.1 9-Valent HPV Vaccine

A 9-valent (Types 6/11/16/18/31/33/45/52/58) human papillomavirus (9vHPV) vaccine was developed to cover 7 cancer-causing HPV types (HPV 16, 18, 31, 33, 45, 52, and 58) which are together responsible for approximately 90% of cervical cancers and HPV-related vulvar, vaginal, and anal cancers, and 2 HPV types (HPV 6 and 11) which are responsible for 90% of genital warts [1, 2, 3, 4, and 5]. In clinical studies, the 9vHPV vaccine prevented infection and disease due to the HPV vaccine types in females 16 to 26 years of age [6]. Key aspects of the 9vHPV vaccine development program are summarized in published literature [7]. The 9vHPV vaccine was licensed in the U.S.A in December 2014, in Canada in February 2015, and in the EU and Australia in June 2015 under the name GARDASIL™9 (Merck & Co., Inc., Kenilworth, New Jersey, U.S.A.). As of December 2016, the 9-valent (Types 6, 11, 16, 18, 31, 33, 45, 52, and 58) HPV L1 VLP vaccine (9vHPV vaccine) was approved under the name GARDASIL®9 in over 40 countries.

The 9vHPVvaccine formulated with Merck Aluminum Adjuvant (amorphous aluminum hydroxyphosphate sulfate) consists of highly purified VLPs of the L1 capsid proteins from HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58. Like for GARDASIL®, the L1 capsid proteins in the vaccine are individually expressed in *Saccharomyces cerevisiae* yeast. The HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 L1 VLPs final aqueous products are comprised of recombinant L1 polypeptides for their respective viral types that have self-assembled into VLPs. Following fermentation, the VLPs are isolated from lysed yeast cells by standard techniques, highly purified, and then adsorbed onto Merck Aluminum Adjuvant (amorphous aluminum hydroxyphosphate sulfate) without the addition of preservative. After preparation of the Monovalent Bulk Adsorbed Products, the bulks are mixed to create the 9vHPVvaccine with the desired concentrations of each monovalent L1 VLP. The 9vHPVvaccine is not a live virus vaccine. It is not capable of causing viral infection.

3.1.2 Rationale for this Study

3.1.2.1 Potential Benefits of Prophylactic HPV Vaccination in Adult Women

Changes in sexual behaviour in the past 30 years characterized by rising age at first marriage and an increase in divorce rates have meant more widespread premarital sexual intercourse and acquisition of new sexual partners around middle age. The potential for HPV infection and disease exists in women in their third, fourth, and fifth decades of life [8]. Studies suggest that the curve of incident high-risk HPV infections is bimodal with a first peak in women under 25 years of age and a second peak after menopause [9]. Older women still experience a substantial burden of HPV-related diseases and are frequently naïve to at least one strain covered by the HPV vaccine. A recent study indicated high acceptance of the vaccine in older women (>26 years) even if the cost of the vaccine had to be self-borne [10].

Clinical studies provide evidence for a potential benefit from the qHPV vaccine GARDASIL® for women older than 26 years of age [8]. The efficacy of GARDASIL® is relevant to GARDASIL®9 since the vaccines are manufactured by a similar process and contain 4 of the same HPV L1 VLPs. The efficacy of GARDASIL®9 was compared with that of the qHPV vaccine with respect to HPV types 6, 11, 16, and 18 in a population of 16- through 26-year-old women (Protocol 001) and in 9- through 15-year-old girls (Protocol 009) [6, 11]. Immune responses for GARDASIL®9 were non-inferior to immune responses for the qHPV vaccine. Of the subjects receiving GARDASIL®9, 99.6% to 100% became seropositive for antibodies against all 9 vaccine types by Month 7 across all groups tested. GARDASIL®9 was also found to be efficacious in preventing HPV 31-, 33-, 45-, 52-, and 58-related persistent infection and disease in girls and women between 16 to 26 years (Protocol 001) [12].

The end-of-study results from a multicentric GARDASIL® study with a median follow-up of 4 years in 3,819 adult women, ages 24 to 45 [13], confirm and extend an interim analysis of this study in establishing that older women without evidence of prior exposure to the vaccine types can benefit from the vaccine [8]. The safety profile in adult women was similar to that seen in younger women, with a somewhat greater number of subjects administered the GARDASIL® vaccine having adverse injection-site experiences versus controls (76.7% versus 64.2%) [13]. The long-term effectiveness and safety (through 6 years) of the GARDASIL® vaccine in older women has also been found to be high [14]. Studies with GARDASIL®9 in women older than 26 years of age have not been conducted.

In several EU countries such as Austria, Italy, Ireland, and Germany, there is acknowledgement of HPV vaccine benefit after HPV exposure and/or treatment. Studies also suggest that subjects who have been previously exposed to HPV might benefit from HPV vaccination [15, 16, 17]. No negative impact was seen in women between 16 and 26 years of age who were seropositive (HPV 16/18) and deoxyribonucleic acid (DNA) positive [18] at the time of vaccination, and vaccine efficacy was seen in women between 16 and 26 years of age who were seropositive (HPV 6/11/16/18) and DNA negative [19]. Results suggest that antibodies elicited by natural infection may not provide complete protection from subsequent HPV reinfection/reactivation and related disease over time in women aged 16 to 26 years, and that the robust immune response to the HPV vaccine may prevent recurrence or reactivation of disease with vaccine HPV types [19].

3.1.2.2 Rationale for the Study Design

An important objective of the GARDASIL®9 (V503) clinical development program is to demonstrate that V503 and GARDASIL® exhibit similar performance with respect to oncogenic HPV types 16 and 18. In the V503 program, the efficacy findings with GARDASIL® will be bridged to V503 based on the demonstration of non-inferior immunogenicity. A primary objective of Protocol V503-001 was to demonstrate that anti-HPV 16 and 18 responses in young women 16 to 26 years of age administered V503 are non-inferior to responses in young women administered GARDASIL®. Similarly, Protocol GDS01C/V503-009 was designed to demonstrate that anti-HPV 16 and 18 responses in subjects 9 to 15 years of age administered V503 are non-inferior to responses in subjects administered GARDASIL®. Protocol GDS07C/V503-020 was designed to accomplish the same objective in young men, 16 to 26 years of age.

Clinical studies provide evidence for a potential benefit from the qHPV vaccine GARDASIL® for women older than 26 years of age [8]. GARDASIL®9 received marketing authorization in the EU in June 2015 for active immunization of females and males from the age of 9 years. This study is designed to assess the safety and immunogenicity of GARDASIL®9 in 27- to 45-year-old women, to complete the evaluation of GARDASIL®9 in the extended age range of female subjects for whom GARDASIL® was proven to be effective. This study is primarily powered to demonstrate the non-inferior immunogenicity of GARDASIL®9 in 27- to 45-year-old women, compared with 16- to 26-year-old women, the population in which GARDASIL®9 has been demonstrated to be effective, with respect to the 7 oncogenic HPV types (Types 16, 18, 31, 33, 45, 52, and 58). The antibody response to the non-oncogenic types HPV 6/11, which are responsible for genital warts, will also be assessed as a secondary objective. The peak of genital warts in females is at 20-24 years. Consequently, although the benefit of vaccinating 27-45 year-old women with a HPV 6/11 vaccine is not negligible, the more clinically relevant part of the vaccine efficacy of GARDASIL®9 in that age range is related to the 7 oncogenic types HPV 16/18/31/33/45/52/58, as reflected in the primary objective.

The choice of the non-inferiority margin is driven by the clinical relevance and the expected variability of the endpoints, and the desired accuracy of the conclusions of the study. A 2-fold non-inferiority margin is considered as appropriate to assess any negative trend in immunogenicity with GARDASIL®9 in 27-45 year-olds women compared with 16-26 year-olds women. Specifically, it is reflecting the fact that the immunogenicity of any HVP vaccines decreases with the increasing age of the subjects making impossible the use of a more stringent non-inferior margin (e.g., 1.5). In addition a more stringent margin is considered to be of limited interest as there is currently no known minimum immunologic correlate for HPV vaccine efficacy, due to high efficacy of the vaccine; such margin would not be expected to add further clinical significance to the results.

This study will include approximately 1,200 women into each of the 2 age groups (27- to 45-year-old subjects and 16- to 26-year-old subjects). Each age group will be further stratified into subgroups of 16- to 20-year-olds and 21- to 26-year-olds for YAW and 27- to 36-year-olds and 37- to 45-year-olds for AW. Enrolment will be monitored to make sure that no single age

stratum (i.e., subgroup) exceeds 55% of the total sample of a given age group (i.e., enrolment in an age stratum will be stopped when around 330 subjects in that age stratum have been vaccinated).

3.1.2.3 Rationale for Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on specimens consented for future biomedical research during this clinical trial. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma) and/or the measurement of other analytes, depending on which specimens are consented for future biomedical research.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective vaccines, and/or to ensure that subjects receive the correct dose of the correct vaccine at the correct time. The details of this Future Biomedical Research sub-trial are presented in Appendix 6.2: Collection and Management of Specimens for Future Biomedical Research.

3.2 Study Procedures

3.2.1 Identifying Study Subjects

Potential study subjects and/or the parent(s)/legal guardian(s) of potential study subjects (for subjects less than 18 years of age, according to specific local regulations [see Section 3.2.2]) will be informed by the investigator about the possibility of their participation in the study. They will be contacted through a telephone call, an invitation letter, an information meeting and/or during a medical visit with the investigator. The study objectives, obligations, benefits and risks will be discussed with potential subjects. The investigator will mention that the participation is voluntary and that withdrawal from the study or non-participation in the study will have no effect on the care to which the subject is otherwise entitled.

3.2.2 Informed Consent

The investigator must obtain documented consent from each potential subject prior to participating in a clinical trial or Future Biomedical Research. If there are changes to the subject's status during the trial (e.g., health or age of majority requirements), the investigator or qualified designee must ensure the appropriate consent is in place.

3.2.2.1 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/IEC requirements, applicable laws and regulations and Sponsor requirements.

Additional ICFs will be obtained in case of a pregnancy occurring during the study to collect data on pregnancy, general data on the baby's health at delivery and complications, if any. The subject or their legal representative must receive a copy of the signed and dated ICF.

3.2.2.2 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 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.

3.2.3 Subject Identification Card

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

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

3.2.4 Concomitant Medication(s)/Treatment(s)

See the exclusion criteria for specific restrictions for prior and concomitant medications at Day 1. Use of medicines and non-study vaccines will be reviewed at each visit and should be documented in the data collection system in the following manner:

- "Special Medications" (corticosteroids, immunosuppressives, immune globulins, and blood products) from 3 days prior to Day 1 through Month 7;
- "Other Medications" from 3 days prior to each study vaccination through 15 days (Day 1 to Day 15) after each study vaccination;
- "Non-Study Non-Replicating (Inactive) Vaccines" for 14 days prior to each study vaccination through 15 days (Day 1 to Day 15) after each study vaccination; and
- "Non-Study Replicating (Live) Vaccines" for 21 days prior to each study vaccination through 15 days (Day 1 to Day 15) after each study vaccination.

If possible, the subject should not receive special medications or non-study vaccines within the time periods given above. Subjects may receive allergen desensitization therapy and tuberculin skin testing while participating in the study.

3.2.5 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 vaccine 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.

3.2.6 Assignment of Allocation Number

A subject who passes screening will be assigned an allocation number from the allocation schedule corresponding to the subject's age group. The allocation number identifies the subject for all procedures occurring afterscreening. Once an allocation number is assigned to a subject, it can never be re-assigned to another subject.

A single subject cannot be assigned more than 1 allocation number.

The allocation number to be obtained from the interactive response technology (IRT) system is a 6 digit number within a pre-specified range of values. The allocation number is assigned just before vaccination and will also be transferred in EDC.

During the Day 1 visit, one may discover a condition that will make the subject ineligible for the study. For example, exclusionary medical conditions mentioned in the inclusion/exclusion questions may be found during limited medical history review. Thus, all pre-vaccination data must be collected and all study procedures must be completed before the subject is assigned an allocation number.

3.2.7 Dispense Electronic Vaccination Report Cards

The vaccination report card was developed to be administered electronically via a hand –held device. This item was structured as recommended in the final FDA Patient Reported Outcome (PRO) Guidance. The investigator or delegate will train the subject or subject's parent/legal guardian in the use of the electronic vaccination report card prior to dispensing it at Visit 1. Oral temperatures, injection-site AEs, eVRC-prompted systemic complaints, other complaints or illnesses, and medications will be recorded on the eVRC throughout the study. The study site personnel will review the data captured on the eVRC with the subject or subject's parent/legal guardian at Visit 2 through Visit 4.

3.2.8 Vaccination and Evaluation

Please review the study flow chart (Section 1.7) for time frames within which to schedule study visits.

3.2.9 Management of Pregnant Subjects

All subjects will have a serum or urine pregnancy test performed before administration of each dose of the study vaccine and at the final Month 7 visit per the manufacturer's instructions.

Any subject with a positive pregnancy test at Day 1 will not be vaccinated and will not be allowed to participate in the study.

For subjects who become pregnant after receiving one or two study vaccinations, study visits and vaccinations will be paused until resolution of the pregnancy (e.g. term, elective termination, spontaneous abortion). Study visits and study vaccination in pregnancy subjects will be handled as described in Table 3. Breastfeeding is not a contraindication to receiving study vaccinations. Pregnancy and breast-feeding in study subjects and infant serious adverse experiences (SAEs) must be reported as described in Section 3.4.

Table 3 Guidelines for Pregnant Subjects: Managing Study Visits and Study Vaccinations

Time When Pregnancy is Detected	Action
Day 1 *(before first vaccination)*	Do not vaccinate subject
Between Day 1 and Month 2 *(After study vaccine dose 1 and before study vaccine dose 2 was administered)*	• No scheduled visits until resolution of the pregnancy (e.g., term, elective termination, spontaneous abortion). • The Month 2 study vaccination should be administered at least 4 weeks following resolution of pregnancy and after normalization of β-hCG levels. • The Month 6 study vaccination should be administered 4 months after the Month 2 study vaccination. • The Month 7 visit should be conducted 1 month after the Month 6 study vaccination. .
Between Month 2 and Month 6 *(After study vaccine dose 2 and before study vaccine dose 3 was administered)*	• No scheduled visits until resolution of the pregnancy (e.g., term, elective termination, spontaneous abortion). • The Month 6 study vaccination should be administered at least 4 weeks following resolution of pregnancy and after normalization of β-hCG levels. • The Month 7 visit should be conducted 1 month after the Month 6 study vaccination.
After Month 6 *(After study vaccine dose 3 was administered)*	• Continue with scheduled study visits during the pregnancy. • Safety follow-up will be conducted after resolution of the pregnancy (e.g., term, elective termination, spontaneous abortion).

3.2.10 Dosage and Administration

Study vaccine will be administered at Day 1, Month 2, and Month 6. At each visit, subjects will receive GARDASIL®9 as a 0.5-mL intramuscular injection using a syringe. Injections should be administered at a 90° angle into the muscle tissue using a needle long enough to ensure intramuscular deposition of vaccine. The deltoid muscle of the non-dominant arm is the preferred site of vaccination. Study vaccines should not be administered into the buttocks area. Injections should not be given within 2 cm of a tattoo, scar, or skin deformity.

The subject should be afebrile (oral temperature <37.8ºC or 100.0°F) for 24 hours prior to each vaccination. If the subject reports having been febrile within this 24-hour pre-vaccination period, no vaccination will be administered to her. The subject should be rescheduled to return for the vaccination visit once the fever has been resolved for at least 24 hours.

If other non-study vaccinations are administered at any time during the study, they should not be administered in the same limb as the study vaccine and must be appropriately documented. The injection site for these non-study vaccines must also be documented.

3.2.11 Future Biomedical Research Samples

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

- DNA for future research
- Leftover main study serum from anti-HPV antibody testing stored for future research

3.2.12 Blinding/Unblinding

Not applicable. This is an open-label study.

3.2.13 General Precautions for Administration of Study Vaccines

Adequate treatment provisions, including epinephrine, should be available for immediate use should any anaphylactic or anaphylactoid reactions occur. The subject should stay at least 15 minutes at the investigator's office to detect any immediate AE.

A sterile syringe and needle should be used for the vaccination injection for each subject. Needles should not be recapped. Safe disposal procedures should be followed.

3.2.14 Discontinuation/Withdrawal Criteria

3.2.14.1 Discontinuation of Vaccination

Discontinuation of study vaccination does not represent withdrawal from the study.

As certain data on clinical events beyond study vaccination discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study vaccination. Therefore, all participants who discontinue study vaccination prior to completion of the vaccination period, will still continue to participate in the trial.

Participants may discontinue study vaccination at any time for any reason or be dropped from the study vaccination at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study vaccination by the investigator or the Sponsor if study vaccination is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons.

A participant must be discontinued from study vaccination but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study vaccination.

For participants who are discontinued from study vaccination but continue to be monitored in the trial, all visits and procedures, as outlined in the trial flowchart, should be completed, except for serum collection for HPV testing at the final visit.

Participants may be allowed to begin study vaccination again if deemed medically appropriate.

3.2.14.2 Withdrawal from the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study vaccination or be followed at scheduled protocol visits.

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the final trial visit should be performed except for serum collection for HPV testing 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 3.4.2 - Assessing and Recording Adverse Events.

3.2.14.3 Withdrawal from Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the subject's consent for Future Biomedical Research will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the subject of completion of withdrawal. Any analyses in progress at the time of request for withdrawal 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 withdrawal cannot be processed.

3.2.14.4 Lost to Follow-up

If a subject fails to return to the clinic for a required study visit and/or if the site is unable to contact the subject, the following procedures are to be performed:

- The site must attempt to contact the subject and reschedule the missed visit. If the subject is contacted, the subject should be counseled on the importance of maintaining the protocol-specified visit schedule.

- The investigator or designee must make every effort to regain contact with the subject at each missed visit (e.g. phone calls and/or a certified letter to the subject's last

known mailing address or locally equivalent methods). These contact attempts should be documented in the subject's medical record.

- Note: A subject is not considered lost to follow up until the last scheduled visit for the individual subject. The amount of missing data for the subject will be managed via the pre-specified data handling and analysis guidelines

3.3 Immunogenicity Measurements

The assay used in this study is the 9-valent HPV cLIA. The purpose of the assay is to detect antibodies to HPV VLPs types 6, 11, 16, 18, 31, 33, 45, 52, and 58, before and after vaccination with GARDASIL®9. Tests will be performed by Focus Diagnostics, Inc. (California, U.S.A) to measure HPV antibodies at baseline and evaluate the serological response after vaccination.

Yeast-derived VLPs are coupled to a set of 9 distinct fluorescent Luminex microspheres. Antibody titres are determined in a multiplexed, competitive format in which known HPV type-specific, phycoerythrin-labelled, neutralising monoclonal antibodies (mAbs) compete with the subject's serum antibodies for binding to type-specific conformationally sensitive, neutralizing epitopes on the VLPs. The fluorescent signals from the bound HPV-specific detection mAbs are inversely proportional to the subject's neutralizing antibody titres. Results for the assay are reported as a concentration of antibody in arbitrary milli-Merck Units per millilitre (mMU/mL).

The HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 cLIA is performed in a 96-well microtitre plate. A 12-point standard curve using reference serum pool from adult females immunized with 9-v HPV vaccine, 4 controls, and 16 samples are added to the plate in duplicate. Samples are tested at a 1:4 and a 1:40 dilution. The detection antibodies followed by the VLP-microspheres for types 6, 11, 16, 18, 31, 33, 45, 52, and 58 are added to each well. The plates are sealed with foil covers and incubated for 15 to 25 hours. Following incubation, the plates are washed and then analysed on a BioPlex (Luminex) instrument.

The seropositivity cutoffs for HPV types are assessed using a panel of sera from subjects that are highly likely to be HPV naïve (children), and from subjects who are likely to be seropositive. Any sample being tested for a specific HPV type with a cLIA titre lower than the cutoff corresponding to that HPV type is considered seronegative for that HPV type.

3.4 Safety Measurements

3.4.1 Clinical Measurements for Safety

All subjects will be observed for at least 15 minutes after each study vaccination for any untoward effects, including allergic reactions. This observation period will be documented in the subject's study chart.

Each subject will receive an electronic VRC at the Day 1, Month 2, and Month 6 study vaccination visits. On the eVRC, the subject or the subject's parent or guardian will be asked to

record oral temperature in the evening after each study vaccination and daily, at the same time of day, for 4 days after each study vaccination for the purpose of identifying febrile events. They will also be asked to record any injection-site reactions prompted in the eVRC, i.e., injection-site tenderness, swelling, or redness occurring after each study vaccination and daily for 4 days after each study vaccination (solicited injection-site reactions). In addition to injection-site reactions prompted in the eVRC, the subject or the subject's parent or guardian will be asked to assess the presence of other injection-site reactions and systemic AEs starting after each study vaccination for a total of 15 days. The subject or the subject's parent or guardian will be asked to record injection-site and systemic AEs, concomitant medications, and concomitant vaccinations on the eVRC.

The information on the eVRC should be generated only by the subject or the subject's parent or legal guardian.. The subject will be expected to bring the eVRC to the study site at the next scheduled visit. In case of hospitalization or visit to another physician, the subject or the subject's parent or legal guardian should be informed to contact the investigator immediately.

The study site personnel will review the data captured on the eVRC with the subject or subject's parent/legal guardian at Visit 2 through Visit 4.

All eVRC information will be recorded in the EDC system. The investigator/sub-investigator will determine causality of systemic AEs recorded on the eVRC using the guidelines given in Section 3.4.2.4 and will classify each event as an SAE or non-serious AE. If an oral temperature indicates a fever (defined as an oral temperature of ≥37.8°C or 100.0°F), the AE of "fever" must be documented in the electronic case report forms (e-CRFs).

At the time of eVRC review at the next scheduled visit, subjects will be questioned regarding any new medical conditions that occurred beyond Day 15 (after dosing). The investigator/sub-investigator will determine if the medical condition is to be reported as an SAE using the reporting guidelines provided below.

3.4.2 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 following the first vaccination(s) and from the time of any subsequent vaccination(s) through 14 days thereafter, and such events will be recorded at each examination on the Adverse Event case report forms/worksheets.

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

In this trial, an overdose is any dose higher than 0.75 mL of vaccine in any one dose or receiving >4 doses (0.5mL each dose).

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.

3.4.2.2 Reporting of Pregnancy and Lactation to the Sponsor

Although not considered an adverse event, it is the responsibility of the investigators or their designees to report any pregnancy in a subject (spontaneously reported to them or detected by urine or serum pregnancy test per protocol) that occurs during the trial through 1 month following the last vaccination. If a subject becomes pregnant during the trial, including subjects who never received vaccine allocation and had a positive pregnancy test at Day 1, all related information must be reported to the SPONSOR. For subjects who become pregnant with LMP prior or equal to Day 30 following the final vaccination, the pregnancy will be collected in the SPONSOR'S global safety database. Furthermore, all fetal loss pregnancy outcomes (ectopic pregnancy, elective termination, spontaneous abortion, late fetal death) must be reported as a

Serious Adverse Experience (Other Important Medical Event). All subjects who receive study vaccine, including discontinued subjects who agree to provide further information, must be followed to the completion/termination of the pregnancy. In addition, if the pregnancy continues to term, the outcome (health of the infant) must be reported.

If a subject receives study vaccine while breastfeeding all related information, including outcome, must be reported to the SPONSOR. Infant serious adverse experiences (SAEs) for all infants born to subjects who received study vaccine must be reported to the SPONSOR.

All pregnancy, lactation, and infant SAE events 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. Refer to Data Entry Guidelines (DEGs) for instructions for reporting these events.

3.4.2.3 Immediate Reporting of Adverse Events to the Sponsor

3.4.2.3.1 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 another important medical event

Refer to Table 4 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 1 month following the last vaccination, 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:

- A death that resulted in the subject discontinuing the trial

or

- 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.

3.4.2.3.2 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 3.4.2.1- 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.

3.4.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events with respect to the elements outlined in Table 4.The investigator's assessment of causality is required for each adverse event. Refer to Table 4 for instructions in evaluating adverse events.

Table 4 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.)	

3.4.2.5 Sponsor Responsibility for Reporting Adverse Events and Patient/Device Events and Incidents

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

3.5 Statistical analysis plan

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to database lock, changes are made to primary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with International Conference on Harmonisation [ICH] Guideline E-9). Changes to exploratory or other non-confirmatory analyses made 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 study. Post hoc exploratory analyses will be clearly identified in the CSR.. All statistical analyses specified in this protocol will be conducted using SAS® Version 9.3 or higher.

3.5.1 In-house Blinding

All subjects in this study will receive GARDASIL®9; the study is thus open-label. However, laboratory personnel conducting HPV assays will be blinded to all subjects' age.

3.5.2 Hypothesis/Estimation

Objectives and hypotheses of the study are stated in Section 2.1.

The study will be considered a success if the non-inferiority criteria for GMTs are met for HPV types 16, 18, 31, 33, 45, 52, and 58 for the comparisons between 27- to 45-year-old women versus 16- to 26-year-old women that received GARDASIL®9.

3.5.3 Analysis Endpoints

3.5.3.1 Immunogenicity

The primary immunogenicity endpoints are the cLIA GMTs to HPV 16, 18, 31, 33, 45, 52 and 58 at 4 weeks after Dose 3.

The secondary immunogenicity endpoints are:

the cLIA seroconversion percentages to HPV 16, 18, 31, 33, 45, 52 and 58 by 4 weeks after Dose 3 in 27- to 45-year-old women.

the cLIA GMTs and the cLIA seroconversion percentages to each of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 by 4 weeks after Dose 3 in 16- to 26-year-old women and 27- to 45-year-old women.

A subject with a cLIA titre at or above the serostatus cutoff for a given HPV type (see Section 3.3) is considered seropositive for that type. Seroconversion is defined as changing serostatus from seronegative at Day 1 to seropositive, by 4 weeks after Dose 3.

3.5.3.2 Safety

Safety assessment will focus on injection-site adverse reactions and elevated temperatures Day 1 to Day 5 post-vaccination and systemic AEs Day 1 to Day 15 post-vaccination, reported on the electronic VRC. In addition, SAEs and pregnancy will be collected from the time the ICF is signed through 1 month following the last vaccination.

3.5.4 Analysis Populations

3.5.4.1 Immunogenicity Analysis Populations

Per Protocol Immunogenicity Population

The per-protocol immunogenicity (PPI) analysis populations will serve as the primary populations of subjects for the analysis of immune responses to each of the 9 HPV types (6, 11, 16, 18, 31, 33, 45, 52, and 58). The PPI analysis populations are HPV type-specific, i.e., each HPV type has its own PPI analysis population. To be included in a particular HPV type-specific PPI analysis population, subjects must:

- Have received all 3 vaccinations of the correct dose of GARDASIL®9 within acceptable day ranges (See Table 5).
- Have evaluable serology results at Day 1 and Month 7 based on serum samples collected within acceptable day ranges (See Table 6).
- Be seronegative to the appropriate HPV type at Day 1.
- Have no protocol deviations that could interfere with the evaluation of subject's immune response to GARDASIL®9.

To be included in the PPI analysis population for HPV 6 and 11, subjects must be seronegative to both HPV 6 and 11 at Day 1. To be included in the PPI analysis population for any other vaccine HPV type, subjects need to be seronegative to that specific type at Day 1. The final determination of protocol deviation categories deemed as having potential to interfere with evaluation of immune response to GARDASIL®9 will be made prior to database lock and will be recorded in a separate study document.

Table 5 Acceptable Day Ranges for Vaccination Visits

Dose of 9vHPV 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 the study vaccine is injected. For vaccinations after Day 1, the day ranges for inclusion in the statistical analysis are wider than the protocol-specified visit windows primarily to account for differences at the study sites in counting months (e.g., 1 calendar month versus 30 days versus 4 weeks).
9vHPV, 9-valent human papillomavirus.

Table 6 Acceptable Day Ranges for Collection of Serum Samples

Study Visit	Target Collection Day (Relative to Day 1[†])	Day Range for Inclusion in Statistical Analysis[†]
Day 1	0	–14 to 0 (Relative to Day 1)[‡]
Month 7	30 days after Dose 3	21 to 49 after Dose 3[§]

[†] Day 1 refers to the date when dose 1 of study vaccine is injected. For Month 7, indicated target collection/day range is relative to date of injection of Dose 3 of study vaccine.
[‡] Applies to both the PPI and ANSS analysis populations.
[§] Applies to the PPI analysis lation only. The day range for the ANSS analysis population is 21 to 105 days after dose 3.
ANSS = All type-specific naïve subjects with serology; PPI = Per-protocol immunogenicity.

All Type-Specific Naïve Subjects with Serology Population

A supportive immunogenicity analysis will be carried out on the all type-specific naïve subjects with serology (ANSS) analysis population. The ANSS analysis populations are HPV type-specific similar to the PPI analysis populations. To be included in these sets of subjects, subjects must:

- Have received all 3 vaccinations of GARDASIL®9;
- Have evaluable serology results at Day 1 and Month 7 based on serum samples collected within acceptable day ranges (See Table 6);
- Be seronegative to the appropriate HPV type at Day 1.

To be included in the ANSS analysis population for HPV 6 and 11, subjects must be seronegative to both HPV 6 and 11 at Day 1. To be included in the ANSS analysis population for any other vaccine HPV type, subjects need to be seronegative to that specific type at Day 1.

Unlike the PPI analysis populations, ANSS analysis populations will not exclude subjects who had protocol deviations deemed as having potential to interfere with evaluation of

immune response to GARDASIL®9. In addition, no day ranges on the timing of the vaccination will be applied.

3.5.4.2 Safety Analysis Population

The all subjects as-treated (ASaT) analysis population, comprised of subjects who received at least 1 dose of GARDASIL®9 and had at least 1 study visit with safety follow-up, will be the primary population for safety analyses.

3.5.5 Statistical Methods

3.5.5.1 Immunogenicity Analyses

The primary hypotheses of non-inferiority of GMTs for the oncogenic HPV types 16, 18, 31, 33, 45, 52, and 58 will be addressed by 7 one-sided tests of non-inferiority (one corresponding to each HPV type) conducted at Type I error α=0.025 (1-sided). For each HPV type, the hypotheses to be tested are:

H_0: $GMT_{AW}/GMT_{YAW} \leq 0.50$

VersusH_1: $GMT_{AW}/GMT_{YAW} > 0.50$

where GMT_{AW} represents the GMTs at Month 7 in 27- to 45-year-old subjects and GMT_{YAW} represents the GMTs at Month 7 in 16- to 26-year-old subjects. The hypothesis testing will be conducted using an ANOVA model with a response of log individual titres and a fixed effect for age group. The statistical criterion for non-inferiority requires that the lower bound of two-sided 95% confidence interval (CI) of GMT ratio (27- to 45-year-old subjects versus 16- to 26-year-old subjects) being greater than 0.50.

It is assumed that the true GMT ratio AW/YAW is 0.7 which is based on the results from V501 Protocol 019 where GMTs were observed to decrease with age at vaccination. The proposed approach (using a non-inferiority margin of 2.0) is appropriate to estimate the GMT ratio and corresponding 95% CIs, and assess any negative trend in immunogenicity with GARDASIL®9 in AW compared to YAW. Moreover, the scientific merit of a non-inferior margin of 1.5 would be limited as there is currently no known minimum immunologic correlate for HPV vaccine efficacy, due to high efficacy of GARDASIL®9; it is not expected to add further clinical significance to the results. A study powered for a more stringent non-inferiority margin would require a substantial increase in sample size which was not deemed necessary for the purpose of this study, based on the immunogenicity data available when this study was designed.

The secondary hypotheses of acceptability of the anti-HPV 16, 18, 31, 33, 45, 52 and 58 seroconversion rates in the 27- to 45-year-old women group will be tested based on the 95% CIs for the single group proportion calculated using the exact binomial method (Clopper-Pearson method) for single proportions. For each HPV type, the statistical criterion for acceptability requires that the lower bound of the 95% CIs of the seroconversion rate for each of the antigens is greater than 90%.

Primary and secondary endpoints (including anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 GMTs and seroconversion rates at 4 weeks after Dose 3) will be summarized within each age group and enrolment strata (16- to 20-year-olds and 21- to 26-year-olds for YAW and 27- to 36-year-olds and 37- to 45-year-olds for AW [Section 2.4.1]) for all subjects in the PPI analysis populations. Furthermore, in order to assess the sensitivity of the results, these analyses will be repeated on the ANSS analysis populations.

In calculations of GMTs by HPV type, cLIA titres reported as less than the Lower Limit of Quantification (LLOQ) of the relevant HPV type will be replaced by the half of the LLOQ in the numerical computation of GMT. No search for outliers will be performed.

In addition, reverse cumulative distribution curves will be provided for graphical comparisons of distributions of HPV titres by age groups.

3.5.5.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by statistical and clinical review of all safety data collected throughout the study. Summaries will be provided for each age group. Statistical analyses of AEs will follow the 3-tiered analysis approach commonly used by the Sponsor when conducting safety assessments, as outlined in Section 2.7.2.

Regardless of incidence, all AEs will be summarized as frequencies and percentages by each age group, by vaccination visit, and across all vaccination visits.

Specific AEs for which summaries will be provided are identified in Table 7.

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

Confidence intervals (95%) and 2-sided p-values will be provided without adjusting for multiplicity.

The method of Miettinen and Nurminen [20] will be used for all comparisons of groups.

Risk differences, CIs, and p-values will be computed across all sites combined (i.e., no stratification by study sites will be performed).

Treatment administration data will be summarized for each age group including number of vaccine injections received. Imputation methods will not be used to replace missing safety data.

Table 7 Analysis Strategy for Safety Parameters

Adverse Event Endpoint	Follow-Up Period: After Any Vaccination Visit: Day 1 to Day 5 (a)	Follow-Up Period: After Any Vaccination Visit: Day 1 to Day 15 (a)	Follow-Up Period: Any Time During Study	Summaries/Analyses: Incidence	Summaries/Analyses: Risk Difference and 95% CI (b)	Summaries/Analyses: p-Value
Clinical AEs						
• Any AE		●		●		
• Deaths			●	●		
Injection-site adverse reactions (c)						
• Injection-site pain/tenderness, swelling, and redness	●			●	●	●
• Other injection-site adverse reactions	●			●	● (d)	
• Severe injection-site adverse reactions	●			●	●	
• Number (%) of subjects by maximum intensity rating, over all injection-site adverse reactions	●			●		
• Number (%) of subjects by maximum intensity rating, within each of the categories of injection-site adverse reactions	●			●		
Systemic AEs						
• Systemic AEs		●		●	● (e)	
• Number (%) of subjects by maximum intensity rating, over all systemic AEs		●		●		
Temperatures						
• Elevated temperatures (f)	●			●	●	●
• Maximum temperatures (g)	●			●		
AEs of Special Interest						
• Serious AEs		●		●	●	
• Serious VR AEs			●	●	●	
• New medical conditions			●	●		

(a) The day of vaccination is counted as Day 1.
(b) Defined as the difference in incidence between the comparison groups.
(c) For the injection-site redness and swelling 0 to 2.5 cm (0 to 1 inch) will be categorized as mild, >2.5 to 5 cm (>1 inch to 2 inches) will be categorized as moderate, and >5 cm (>2 inches) will be categorized as severe.
(d) Only for injection-site adverse reactions occurring in ≥1% of subjects in either group.
(e) Only for systemic AEs occurring in ≥1% of subjects in either group.
(f) Defined as maximum (over the follow-up period) temperature ≥37.8°C (≥100°F, oral equivalent).
(g) Distribution of maximum temperatures over the relevant follow-up period.
AEs, adverse events; VR, vaccine-related.

3.5.5.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

Baseline characteristics and demographic variables will be summarized by age groups using descriptive statistics or categorical tables on all subjects enrolled in the study and on all PPI-eligible subjects (i.e., subjects belonging to at least one PPI analysis populations). No formal statistical testing of differences between age groups with respect to these characteristics will be performed.

Quantitative variables (except antibody titres) will be displayed using descriptive statistics by way of sample size, mean, standard deviation, median, minimum, and maximum. Antibody titres will be displayed using descriptive statistics by way of sample size, GMTs, and two-sided 95% CIs.

Categorical variables will be displayed using descriptive statistics by way of sample size, count by category, and proportion by category. Missing data will be counted but not included in the calculation of proportions.

Subject Accounting

The number and percentage of subjects screened (ICF signed), enrolled (allocation number assigned), vaccinated (at least once and at each vaccination time point), discontinued, and the primary reason for discontinuation will be displayed by age group. Reasons for subjects excluded from the PPI analysis populations will be summarized and displayed in subject accounting tables. A summary of subjects screened/vaccinated by country/site will be provided.

Subject Characteristics

Demographic variables and other baseline characteristics such as age, vital signs (height, weight, and oral temperature), and country will be summarized by strata and age group.

Baseline HPV Status

A serum sample will be collected from all subjects at the Day 1 visit for the purpose of assessing baseline HPV serostatus to the 9vHPVvaccine HPV types (HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58). A subject will be considered seropositive to a given HPV type at Day 1 if the subject's anti-HPV titre is greater than or equal to the corresponding serostatus cutoff for that HPV type or seronegative to a given HPV type at Day 1 if the subject's anti-HPV titre is less than the corresponding serostatus cutoff for that HPV type. For each HPV type, the proportions of subjects who are seronegative or seropositive will be summarized by strata and age group.

Prior and Concomitant Medications

The number and percentage of subjects with prior medications or vaccinations prior to each study vaccination will be summarized for each age group. The relevant pre-injection day

ranges for summarization will be 3 days for medications, 14 days for non-live virus vaccines, and 21 days for live virus vaccines.

Similarly, the number and percentage of subjects with concomitant medications or vaccinations within 15 days (Day 1 to Day 15) following any study vaccination will be summarized for each age group. The number of subjects with "Special Medications" (corticosteroids, immunosuppressives, immune globulins, and blood products [Section3.2.4]) will be summarized for each age group throughout the study period.

New Medical Conditions: New medical conditions occurring during the study (i.e., incident medical conditions occurring outside of a Day 1 to Day 15 period post-vaccination and not considered SAEs) will be summarized for each age group.

3.5.6 Multiplicity

For the primary hypotheses, success requires that non-inferiority be established for all oncogenic HPV types (i.e., 16, 18, 31, 33, 45, 52, and 58); thus, no multiplicity adjustment is necessary for this study.

3.5.7 Sample Size and Power Calculations

3.5.7.1 Sample Size and Power for Immunogenicity Analyses

This study will include approximately 1,200 women into each of the 2 age groups (27- to 45-year-old subjects and 16- to 26-year-old subjects).

The power of the study was calculated using SAS Version 9.3 based on the assumption of log-normality of the post-vaccination titres.

The analysis of the immunogenicity endpoints will follow a Per Protocol approach. In the scope of the study, i.e., an immunogenicity study with a 3-dose HPV vaccination schedule on women 16- to 45-years of age, the rate of dropout and general protocol deviations deemed as having potential to interfere with evaluation of immune response to GARDASIL®9 leading to exclusion from the per protocol analysis is expected to be less than 15%. Based on a previous study conducted with GARDASIL® in 24- to 45-year-old women (Study V501 Protocol 019), it is assumed that 10 to 20% of enrolled subjects would be seropositive at baseline for a given HPV type. This would lead to an overall rate of exclusion from the PPI analysis populations ranging from 25% to 35% of enrolled subjects. Given these exclusion rates, starting with 1,200 enrolled subjects (600 per age group), Table 8 shows the number of evaluable subjects and the corresponding power for one single comparison depending on the percentage of subjects excluded from the PPI analysis populations.

Table 8 Study Power Depending on Exclusion Rates

Number of enrolled subjects per group	Estimated percentage of subjects excluded from the PPI Sets	Number of evaluable subjects per group	Standard deviation (natural log scale)	Expected GMT ratio AW/YAW	Power for one single comparison
600	35%	390	1.2	0.7	0.97
600	25%	450	1.2	0.7	0.99

AW, adult women; GMT, geometric mean titre; PPI, per protocol immunogenicity; YAW, young adult women.

The expected GMT ratio AW/YAW is 0.7, reflecting the fact that the immunogenicity of any HVP vaccines decreases with the increasing age of the subjects. It is to be noted that the study may result in an upper bound of the two-sided 95% CI around the GMT ratio AW/YAW being lower than 1, although the non-inferiority would be demonstrated if the lower bound is greater than 0.5 (i.e., the non-inferiority margin). If 1,200 subjects are enrolled in the study in a 1:1 fashion with regards to the 2 age groups, the evaluable population will range from 780 to 900 subjects. If the exclusion rate from the Per Protocol analysis is 35% for 1 HPV type and 25% for the 6 others, this study will have over 90% power to rule out a 2-fold decrease in GMT for the 7 oncogenic HPV types (Types 16, 18, 31, 33, 45, 52, and 58). The power calculation is based on an estimate of 1.2 for the variability of each serotype on the natural log scale and assumes that the true GMT ratio AW/YAW is 0.7 which is based on the results from Study V501 Protocol 019 where GMTs were observed to decrease with age at vaccination.

Assuming a true seroconversion rate to each HPV type >98% and a percentage of subjects excluded from the PPI analysis populations <35% for HPV 16 and <25% for HPV 18, 31, 33, 45, 52, and 58, the power of the secondary hypothesis testing is >99% using Type I error α=0.025 (one-sided).

3.5.7.1.1 Sample Size and Power for Safety Analyses

The probability of observing at least 1 vaccine-related SAE in this study depends on the number of subjects vaccinated and the underlying incidence rate in the study population. Table 9 shows the probability of observing at least one vaccine-related SAE within the 1,200 subjects who will receive GARDASIL®9 for various theoretical incidence rates.

Table 9 Probability of Observing At Least One Vaccine Related Serious Adverse Event for Various Theoretical Incidence Rates

Incidence Rates	Probability of at Least 1 Serious Adverse Event
1.0%	99%
0.5%	99%
0.1%	70%
0.05%	45%
0.01%	11%

If no vaccine related SAE is observed in the 1,200 subjects who will receive GARDASIL®9 in this study, there is a 99% probability that the true incidence rate is <0.39%.

3.5.8 Interim Analysis

No interim analysis is planned.

3.6 DEFINITION OF COMPLIANCE MEASURE

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

3.7 Labeling, Packaging, Storage, Dispensing, and Return of Clinical Supplies

3.7.1 Product Description

Investigational Medicinal Product (IMP) will be provided by the Sponsor as summarized in Table 10.

Table 10 Investigational Medicinal Product

Product Name	Potency	Dosage Form/ Contents/Route of Administration	Storage Conditions
GARDASIL®9 V503 (9-Valent HPV L1 VLP) Vaccine (Recombinant, adsorbed)	**HPV Types (L1 protein)** **6/11/16/18/31/33/45/52/58** 30/40/60/40/20/20/20/20/20 mcg Adsorbed on AAHS 500 mcg	Sterile suspension for intramuscular injection 1 dose (0.5 mL) Shake well before use.	Store at 2.0 to 8.0°C (35.6°F and 46.4°F). Do not freeze. Protect from light.
AAHS, Merck Aluminum Adjuvant (amorphous aluminum hydroxyphosphate sulfate); HPV, human papillomavirus; VLP, virus-like particle.			

GARDASIL®9 is available as a suspension for injection. It appears as a clear liquid with white precipitate.

3.7.2 Packaging Information

Supplies will be labelled in accordance with local regulatory requirements.

3.7.3 Clinical Supplies Disclosure

Not applicable. This study is open-label.

3.7.4 Shipment of Investigational Medicinal Product

The IMP will be shipped to the study sites, refrigerated and stored at 2.0°C to 8.0°C (35.6°F to 46.4°F). Upon receipt at the study site, the vaccine should be removed from the outer secondary shipping box and placed immediately into the refrigerator.

Each shipment will include an electronic temperature-monitoring device to verify maintenance of the cold chain during transport, as well as an Acknowledgement of Receipt form.

Upon arrival of the shipment at the study site, the person responsible will verify that the content of the shipment corresponds to the order and that the products arrived in good condition. He/she will acknowledge receipt in IRT, For temperature excursions noted via the device, the temperature data recorded during shipment will be downloaded the current customer complaint process should be followed to acknowledge the excursions

3.7.5 Storage and Handling Requirements

For details on storage and handling requirements, please see Section 3.7.5.. The storage conditions will be indicated on the product label.

The clinical supplies storage area at the study site must be monitored by the site staff for temperature consistency with the acceptable storage temperature range specified in this protocol or in the product label attached to the protocol. Documentation of temperature monitoring should be maintained. Supplies should be stored in the original nested box with the lid closed to minimize exposure to light. If the refrigerator in which the study vaccine is stored deviates from the 2.0°C to 8.0°C range (35.6°F to 46.4°F), study vaccinations should be suspended and the Sponsor (or designee) should be contacted immediately. Vaccine must NOT be frozen.

A daily refrigerator temperature log must be maintained at the study site. The refrigerator must be equipped with an appropriately calibrated min/max thermometer and/or circular chart temperature recorder. The temperature log will be reviewed by the Clinical Research Associate (CRA) throughout the study. An appropriate back up system (i.e., alarm or generator) and study site personnel telephone numbers should be in place in the event of a refrigerator failure.

In case of a cold chain break (i.e., if the temperature of the refrigerator is lower than 2.0°C or exceeds 8.0°C [lower than 35.6°F or exceeds 46.4°F]):

The investigator (or designee) at the site should follow the current clinical complaint process to file an excursion

The investigator (or designee) must wait for further instructions from the Sponsor or from the CRA, as to whether or not the study vaccines can be used. The investigator is not allowed to use the study vaccines before getting the Sponsor (or designee) approval to do so.

The cold chain break must be documented in the Investigator Site File and in the Trial Master File.

The IMP must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. IMP is to be administered only in accordance with the protocol.

Any concerns raised about the manufacturing, packaging, labelling, or distribution of IMP supply which could potentially impact its suitability for use should be immediately reported to the Sponsor. The IMP must be quarantined until the Sponsor feed-back is received as to whether or not the vaccine can be used.

Unused study vaccines taken out from the stock at study site are considered to be unusable and cannot be returned to the stock. They must be quarantined and returned back to the Sponsor (or designee) as soon as possible.

3.7.6 Accountability of Investigational Medicinal Product

For the accountability procedure, please refer to Guidelines for IMP Management on site.

3.7.7 Return of Investigational Medicinal Product

All empty primary containers will be destroyed at the study site according to local regulations. Supplies will need to be returned to the depot of origin if destruction is not possible locally.

Empty boxes of study vaccines must be kept at study site to enable verification of the vaccine accountability by the CRA (or designee) and can afterwards be destroyed on site.

The following should be returned to the distributor according to the procedures detailed in the Investigator Site File:

Study vaccines unusable following a cold chain deviation, as soon as possible;

Study vaccines expiring within the current month, immediately;

Unused study vaccines which remain in stock at study site after the last administration to the last subject of the corresponding study site, after verification of vaccine accountability;

Study vaccines concerned by a batch recall, immediately.

The CRA (or designee) will organise the return of unusable and unused study vaccines, which should be returned by ambient transport. The list of the returned study vaccines should be enclosed in the returned package. For the return procedure, please refer to Guidelines for IMP Management on site. The distributor will confirm the receipt of each study vaccine returned (at unit level).

3.8 Data Management

Study data will be acquired via electronic format. As part of their responsibilities, the principal investigator or sub-investigator agree to maintain adequate case histories for the subjects treated as part of the research under this protocol. The principal investigator or sub-investigator agree to maintain source documentation (e.g., laboratory reports), to enter subject data into the e-CRF as accurately as possible, and to respond to any reported discrepancies rapidly.

Each e-CRF will allow data entry by study site staff that can add and edit data, identify and resolve discrepancies, and view records. This system provides immediate direct data transfer to the database, as well as immediate detection of discrepancies, enabling study site coordinators to resolve and manage discrepancies in a timely manner.

Each person involved with the study will have an individual user name and password that allows for record traceability. Thus, the system, and subsequently any investigative reviews, can identify coordinators, investigators, and individuals who have entered or modified records, as well as the time and date of any modifications. A quality review of the data will

be performed by the study site with additional reviews by the clinical monitor through source data verification.

3.9 Biological Specimens

Information regarding biological specimens for this protocol will be provided by the Sponsor. Please see the Investigator Site File for further details.

4.0 ADMINISTRATIVE AND REGULATORY DETAILS

4.1 Confidentiality

4.1.1 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.

4.1.2 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.

4.1.3 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.

4.1.4 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC 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.

4.2 Compliance with Financial Disclosure Requirements

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

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

4.3 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 sponsor, is provided in Section 6.1 - Merck Code of Conduct for Clinical Trials.

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

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

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

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

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

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

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

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

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

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site is open in an EU country, 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 Protocol/CSR 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.

4.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. The Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Sponsor entries are not limited to FDAAA or the EMA clinical trial directive 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 FDAAA, the EMA clinical trials directive or other locally mandated registries are that of the

Sponsor and agrees not to submit any information about this trial or its results to those registries.

4.5 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.

4.6 Data Management

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

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

4.7 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. The Sponsor 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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6.0 APPENDICES

6.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Subject Protection

A. IRB/ERC review

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

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

6.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens consented and/or collected in this trial as outlined in Section 3.2.11 – Future Biomedical Research Samples will be used in various experiments to understand:

- The biology of how vaccines work
- Biomarkers responsible for how a vaccine enters and is removed by the body
- Other pathways vaccines may interact with
- The biology of disease

The specimen(s) may be used for future assay development and 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 vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

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

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the subjects on the visit designated in the trial flow chart. If delayed, present consent at next possible Subject Visit. Consent

forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons.

A template of each trial site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen(s)

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

4. **Confidential Subject Information for Future Biomedical Research**

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

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

At the clinical trial site, unique codes will be placed on the Future Biomedical Research specimens. This 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 unique code will be held at the trial site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage

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

6. Withdrawal from Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and ask that their biospecimens not be used for Future Biomedical Research. Subjects may withdraw

consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the subject's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for Future Biomedical Research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the subject of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/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 withdrawal of consent and/or destruction cannot be processed.

7. Retention of Specimens

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

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

8. Data Security

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

9. Reporting of Future Biomedical Research Data to Subjects

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

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and subjects. Subjects will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

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

11. Risks versus Benefits of Future Biomedical Research

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

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

12. Questions

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

13. References

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
3. Industry Pharmacogenomics Working Group. Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/
4. Industry Pharmacogenomics Working Group. Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

6.3 Approximate Blood/Tissue Volumes Drawn/Collected by Trial Visit and by Sample Types

Trial Visit	Day1 Visits 1	Month 2 Visit 2	Month 6 Visit 3	Month 7 Visits 4
Blood Parameter	**Approximate Blood Volume (mL)**			
Serum β-Human Chorionic Gonadotropin (β-hCG)[a]	1ml	1ml	1ml	1ml
Serum for Anti-HPV antibody testing	10ml	NA	NA	10ml
Blood (DNA) for Future Biomedical Research	8.5ml	NA	NA	NA
Expected Total (mL)	19.5ml	1ml	1ml	11ml
a. Serum collection for β-hCG is only for subjects who get serum pregnancy test				

7.0 SIGNATURES

7.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

7.2 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 3.4.2 – TRIAL PROCEDURES (Assessing and Recording Adverse Events). I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	