26 March 2015
EMA/CHMP/76591/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Gardasil 9

International non-proprietary name: human papillomavirus 9-valent vaccine (RECOMBINANT, ADSORBED)

Procedure No. EMEA/H/C/003852/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Name of the medicinal product:	Gardasil 9
Applicant:	Sanofi Pasteur MSD SNC 162 Avenue Jean Jaurès 69007 Lyon France
Active substance:	human papillomavirus type 6 L1 protein human papillomavirus type 11 L1 protein human papillomavirus type 16 L1 protein human papillomavirus type 18 L1 protein human papillomavirus type 31 L1 protein human papillomavirus type 33 L1 protein human papillomavirus type 45 L1 protein human papillomavirus type 52 L1 protein human papillomavirus type 58 L1 protein
Common Name:	human papillomavirus 9-valent vaccine (recombinant, adsorbed)
Pharmaco-therapeutic group (ATC Code):	J07BM03
Therapeutic indication(s):	Gardasil 9 is indicated for active immunisation of individuals from the age of 9 years against the following HPV diseases: • Premalignant lesions and cancers affecting the cervix, vulva, vagina and anus caused by vaccine HPV types • Genital warts (Condyloma acuminata) caused by specific HPV types.
Pharmaceutical form(s):	Suspension for injection
	Per 0.5 ml dose: Human Papillomavirus Type 6 L1

Strength(s):	protein 30 micrograms Human Papillomavirus Type 11 L1 protein 40 micrograms Human Papillomavirus Type 16 L1 protein 60 micrograms Human Papillomavirus Type 18 L1 protein 40 micrograms Human Papillomavirus Type 31 L1 protein 20 micrograms Human Papillomavirus Type 33 L1 protein 20 micrograms Human Papillomavirus Type 45 L1 protein 20 micrograms Human Papillomavirus Type 52 L1 protein 20 micrograms Human Papillomavirus Type 58 L1 protein 20 micrograms
Route of administration:	Intramuscular use
Packaging:	vial (glass) or pre-filled syringe
Package size(s):	Pack of 1 vial Pack of 1 syringe + 2 needles Pack of 10 syringes + 20 needles

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List of abbreviations

9vHPV vaccine	Nine-valent Human Papillomavirus vaccine
AE	Adverse experience
AIN	Anal intraepithelial neoplasia
AIS	Adenocarcinoma in situ
ANSS	All (HPV Type-specific) Naïve Subjects with Serology
ASC-H	Atypical squamous cells cannot rule out HSIL
ASC-US	Atypical squamous cells of undetermined significance
CI	Confidence interval
CIN	Cervical intraepithelial neoplasia
cLIA	Competitive Luminex Immunoassay
CRF	Case report form
DSMB	Data and Safety Monitoring Board
EGLs	External genital lesions
ELISA	Enzyme-linked immunosorbent assay
FAS	Full Analysis Set
FMP	Final Manufacturing Process
GMR	Geometric mean ratio
GMTs	Geometric Mean Titres
HN-TS	HPV-Naïve Type-Specific
HPV	Human Papillomavirus
HR	High-risk
HSIL	High-Grade Squamous Intraepithelial Lesion
LR	Low-risk
Pap	Papanicolaou
PBNA	Pseudovirion-based neutralization assay
PPE	Per Protocol Efficacy
PPI	Per Protocol Immunogenicity
qHPV vaccine	Quadrivalent Human Papillomavirus vaccine
RR	Risk reduction
SAEs	Serious Adverse Experiences
SCC	Squamous cell carcinoma
VaIN	Vaginal Intraepithelial Neoplasia
VE	Vaccine efficacy
VIN	Vulvar Intraepithelial Neoplasia
VLP	Virus-Like Particle

1. Background information on the procedure

Submission of the dossier

The applicant Sanofi Pasteur MSD SNC submitted on 3 March 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Gardasil 9, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 19 September 2013

The applicant applied for the following indication:

Gardasil 9 is indicated for active immunization from the age of 9 years against the following HPV diseases:
• cervical cancer and premalignant cervical lesions
• vulvar and vaginal cancers and premalignant vulvar and vaginal lesions
• external genital warts caused by HPV types (6, 11, 16, 18, 31, 33, 45, 52, 58).

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that Human Papillomavirus Type 31 L1 protein, Human Papillomavirus Type 33 L1 protein, Human Papillomavirus Type 45 L1 protein, Human Papillomavirus Type 52 L1 protein and Human Papillomavirus Type 58 L1 protein were considered to be new active substances.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0196/2013 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0196/2013 was completed. The PDCO issued an opinion on compliance for the PIP P/0196/2013.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substances Human Papillomavirus Type 31 L1 protein, Human Papillomavirus Type 33 L1 protein, Human Papillomavirus Type 45 L1 protein, Human Papillomavirus Type 52 L1 protein and Human Papillomavirus Type 58 L1 protein contained in the above medicinal product to be considered as a new

active substances in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 26 June 2008 and 17 November 2011. The Scientific Advice pertained to clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

Manufacturers

Manufacturer responsible for batch release

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP:

Rapporteur: Kristina Dunder

Co-Rapporteur: Jan Mueller-Berghaus

- The application was received by the EMA on 3 March 2014.
- The procedure started on 26 March 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 June 2014. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 15 June 2014.
- During the meeting on 10 July 2014 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan
- During the meeting on 24 July 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 24 July.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 16 October 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 25 November 2014.
- During the meeting on 4 December 2014 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan
- During the CHMP meeting on 18 December 2014, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 23 February 2015.

- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding issues to all CHMP members on 03 March 2015.
- During the meeting on 12 March 2015 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan
- During the meeting on 23 to 26 March 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Gardasil 9.

2. Scientific discussion

Introduction

2.1. Problem statement

HPV infection causes benign and malignant dysplastic disease, localized primarily in the anogenital area and aerodigestive tract, in both men and women. Persistent HPV infection significantly increases the risk of cervical and other anogenital cancers, and oropharyngeal cancers. Overall, HPV is responsible for approximately 5% of the global cancer disease burden.

Cervical Cancer and Precancerous Dysplasia. Nearly 100% of cervical cancers are caused by HPV infection. Cervical cancer is the second most common cancer in women worldwide, with approximately 530,000 new cases diagnosed each year and 275,000 deaths annually. Most (approximately 80%) of the cases occur in developing countries. In developed countries, cervical cancer screening programs have reduced the incidence of cervical cancer by 75% due to the detection, follow-up, and treatment of premalignant lesions. Despite this success, nearly 12000 cases of cervical cancer still occur annually in the United States, causing over 4000 deaths annually. In the European Union (EU 28), about 34000 new cervical cancer cases are diagnosed every year and cause about 13000 annual death. About 55000 new cervical cancer are estimated to occur each year in Europe (United Nation definition).

Non-Cervical HPV Disease. Infection with HPV is also associated with anal, vulvar, vaginal, penile, and oropharyngeal cancers. Each of the HPV-related diseases is much less frequent than cervical cancer, but taken together, they represent a significant human health and economic burden. Of particular concern, the incidence of anal cancer has been increasing in both men and women over the past several decades. The incidence of HPV-associated oropharyngeal cancer is also increasing. It is anticipated that oropharyngeal cancers could soon become the dominant HPV-associated cancer in developed countries, where cervical cancer incidence has decreased because of screening programs. In Europe, for example, approximately 90% of anal cancers, 15% of vulvar cancers, 70% of vaginal cancers, and 30 to 40% of penile cancers are estimated to be caused by HPV infection; in addition, about 16000 new non-cervical HPV-related anogenital cancer cases are diagnosed in men and women every year. In the United States, the annual incidence of HPV-associated oropharyngeal cancer is now comparable to that of cervical cancer, and affects both men and women, with a male:female ratio of approximately 4:1. Increasing trends of head and neck cancers at sites considered associated with HPV have also been observed in Europe. Between 26-40% of oropharyngeal cancers are estimated to be caused by HPV infection in Europe. Approximately 8100 new HPV-related oropharyngeal cancer cases are estimated to be diagnosed every year in Europe.

Benign HPV Disease. Infection with HPV also cause benign lesions like Condyloma Acuminata (anogenital Warts: GW) located in the genital or perianal region and juvenile recurrent respiratory papillomatosis (RRP)

primarily located in the larynx. RRP is rare but can be life-threatening and is thought to occur by transmission of the virus from an infected mother to her child. Treatment of these benign lesions is often lengthy and painful; RRP often has high recurrence rate. In Europe, incidence rate of GW is estimated to vary between 150 and 170 per 100 000 person-year in the general population, and is generally found to be highest among 20-24 years old individuals and was evaluated to vary between 450 and 700 per 100 000 within this age group.

HPV types are classified into high-risk (HR) types, based on their potential to cause cancer, and low-risk (LR) types (causing generally benign lesions). The International Agency for Research on Cancer (IARC) has identified 12 HPV types as carcinogens. These include the 7 HR HPV types represented in the 9vHPV vaccine (HPV 16, 18, 31, 33, 45, 52, and 58) and 5 HR HPV types not represented in the 9vHPV vaccine (HPV 35, 39, 51, 56, and 59). LR HPV types 6 and 11, which are responsible for ~90% genital warts and RRP cases, are also included in the 9vHPV vaccine. A summary of the attribution of the 9vHPV vaccine types to cervical lesions worldwide is provided in the table below:

	Attribution		
Lesion Type	**6/11/16/18**	**31/33/45/52/58**[†]	**Overall 9V**
Cervical Cancer	70%	20%	**90%**
AIS	95%	<5%	**>95%**
CIN 2/3	50%	30%	**75-85%**
CIN 3	55-65%	25-30%	**85-90%**
CIN 2	40%	30-35%	**70-75%**
CIN 1	30-35%[‡]	25%	**50-60%***

[†] In absence of HPV types 6/11/16/18
[‡] HPV 6/11 are attributed to ~5% of CIN1 lesions.

2.2. About the product

The 9vHPV vaccine Gardasil 9 is a vaccine against HPV, and can be considered an extended version of the quadrivalent Gardasil (qHPV). The 9vHPV vaccine targets HPV Types 6, 11, 16, and 18 (named throughout the report as old types, since they are also targeted by the licensed qHPV vaccines Gardasil and Silgard) as well as HPV Types 31, 33, 45, 52, and 58 (named throughout the report as new types). The quadrivalent HPV vaccine used in the context of Gardasil 9 dossier is referenced to as qHPV or Gardasil in this report.

The Human Papillomavirus 9-Valent Vaccine (named 9-vHPV vaccine or Gardasil 9 in this report) is a sterile, white, cloudy, liquid suspension prepared from the HPV Type 6, HPV Type 11, HPV Type 16, HPV Type 18, HPV Type 31, HPV Type 33, HPV Type 45, HPV Type 52, and HPV Type 58 Monovalent Bulk Adsorbed Products (MBAPs). It is filled into single-dose vials or syringes to ensure a minimum recoverable volume of 0.5 mL for injection.

The HPV L1 VPLs are produced using the same manufacturing process as used for the applicant's licensed Gardasil (also called qHPV in this report). The VLPs are adsorbed on amorphous aluminum hydroxyphosphate

sulfate (AAHS) adjuvant, with the final formulation also including sodium chloride, L-histidine, polysorbate 80, sodium borate, and water for injection.

Each 0.5-mL dose of 9vHPV vaccine is formulated to contain 500 µg AAHS and 30/40/60/40/20/20/20/20/20 µg of HPV 6/11/16/18/31/33/45/52/58 L1 proteins respectively. The final container is a sterile suspension for injection in a single-dose vial or a prefilled syringe.

Gardasil 9 is intended for intramuscular injection, and the primary series consists of 3 separate 0.5 ml doses administered according to the following schedule: 0, 2, 6 months. If an alternate vaccination schedule is necessary, the second dose should be administered at least one month after the first dose and the third dose should be administered at least 3 months after the second dose. All three doses should be given within a 1-year period.

Gardasil 9 is indicated for active immunization from the age of 9 years against the following HPV diseases caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, 58: (1) cervical cancer and premalignant cervical lesions; (2) vulvar and vaginal cancers and premalignant vulvar and vaginal lesions; (3) premalignant anal lesions and anal cancers; (4) external genital warts.

Quality aspects

2.2.1. Introduction

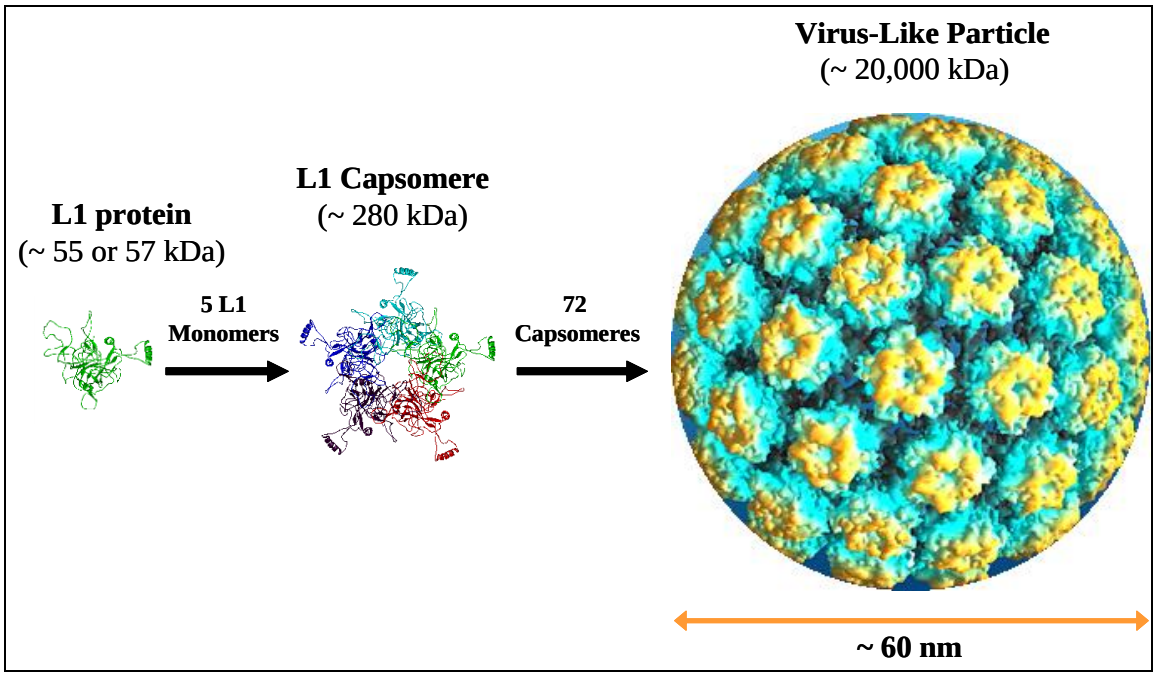
Papillomaviruses, which are small, non-enveloped, icosahedral DNA viruses, are classified according to their L1 DNA sequence homology. The nine HPV types in the 9-Valent HPV Vaccine are HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58.

The drug substance consists of the nine Monovalent Bulk Adsorbed Products (MBAPs), one for each of the nine human papillomavirus (HPV) types included in Human Papillomavirus 9-Valent Vaccine, Recombinant (9-Valent HPV Vaccine). The individual VLPs of each type are adsorbed onto amorphous aluminium hydroxyphosphate sulfate adjuvant. The active components in each MBAP are the highly purified virus-like particles (VLPs) made up of the recombinant major capsid (L1) protein for that HPV type. L1 is the major structural protein of the human papillomavirus viral capsid.

2.2.2. Active Substance

General information

Native papillomavirus virions have an icosahedral symmetry consisting of 72 pentamers of L1 protein and are nearly spherical with an approximate diameter of 60 nm. For the vaccine, the L1 capsid polypeptide of each of the nine vaccine types is expressed in a separate fermentation of a recombinant strain of *Saccharomyces cerevisiae*, and self-assembles to form VLPs, which mimic the capsid structure of the native virions. See Figure: Structural model of a full size HPV Virus-Like Particle.



Structural Model of a full-size HPV Virus-Like Particle.

The image used to represent the VLP is from Y. Modis et al[1]

Manufacture, characterisation and process controls

Manufacture

The drug substance is manufactured at one of two Merck Sharp & Dohme sites in the USA; the WestPoint site or the Stonewall site. Sufficient information to confirm the GMP status of the two manufacturing sites has been provided. Both sites are included as a manufacturer of drug substance for the approved product Gardasil.

The approved product Gardasil and Gardasil 9 contain the same 4-valent (Types 6, 11, 16, and 18) HPV drug substance materials. The manufacturing process/ controls for these 4-valent types are largely the same.

The manufacture of the drug substance consists of two main steps:

Fermentation and harvest of the recombinant yeast cell slurry

The fermentation process is conducted in two steps, the seed fermentation followed by the production fermentation, which includes a cell expansion and a galactose induction phase to produce L1 protein. At the end of the fermentation phase, the cells are harvested by diafiltration to produce the cell slurry, which is dispensed and frozen at <-60°C until further processing. For Types 31, 33, 45, 52 and 58, a protease inhibitor is added to the cell harvest to prevent proteolytic cleavage of the L1 protein during purification. Two different fermentation scale productions have been established at the different manufacturing sites. The Stonewall fermentation process is 2 times that of West Point. The purification of the VLPs and the manufacture of the MBAPs are in the same range at both sites.

Purification of the VLPs and adsorption of the purified VLPs onto aluminium-containing adjuvant to form the Drug Substance (MBAP).

[1] Modis Y, Trus BL, Harrison SC. Atomic model of the papillomavirus capsid. EMBO J 2002;21(18):4754-62.

The purification process for Types 31, 33, 45, 52 and 58 was established based on the already approved processes of Types 6, 11, 16 and 18.

Cell slurry is thawed and then homogenised to release VLPs from yeast cells. The purification of the VLPs and the manufacture of the MBAP are identical at both sites. The purification is conducted by multiple steps employing cross-flow membrane filtration steps (initial step removes cell debris), cation exchange (further removal of host cell proteins, HCP) and hydroxyapatite chromatography (polishing step to remove HCP, nucleic acids, lipids and residual proteases; it also selects for smaller, monodisperse populations of HPV VLPs). The columns are validated for reuse for subsequent lots of the same HPV type, and regeneration procedures are described.

For all HPV Types except 18, the VLPs are disassembled using dithiothreitol (DTT) and then reassembled by removing dithiothreitol by diafiltration. The purpose of the disassembly and reassembly steps is to improve VLP structure and stability. Type 18 VLPs do not require disassembly and reassembly because they are inherently more stable.

The final steps in the purification process for all types are buffer exchange and sterile filtration to produce the final aqueous product (FAP). The FAP is diluted to a target protein concentration of 640 µg/ml. The diluted FAP (DFAP) may be stored for 7 days at 2-8°C.

The FAP for each type is then adsorbed onto amorphous aluminium hydroxyphosphate sulfate to produce the MBAP. The purpose of the adsorption step is to provide a stable, immunogenic formulation of HPV MBAP. Each DFAP is individually added to the adjuvant with in-line mixing. Target protein concentration in the MBAP is 320 µg/ml. The MBAP for each type is filled in glass bottles with sanitary fittings and then stored at 2-8°C.

The amorphous aluminium hydroxyphosphate sulfate adjuvant used in the manufacture of the MBAP is manufactured at the same sites as the drug substance.

The manufacturing process is well defined, extensively characterised and acceptably validated. Information on the composition of buffers, solutions and raw materials used in manufacturing has been provided. Appropriate control strategies are employed to confirm consistent production. Critical process parameters have been defined for fermentation of individual HPV types (mainly related to galactose addition rate/ concentration, protease inhibitor concentration and harvest time). Critical process parameters for purification steps have been described (including DTT concentration, blending ratio of adjuvant and DFAP). However, the proposed regulatory strategy to manage changes in non-critical parameters was asked for in the initial assessment and the applicant has sufficiently clarified the handling during the procedure. Furthermore, minor issues were outstanding in the initial application, e.g. pre-filtration bioburden limits, nature of bags used to store cell slurry. These have also been resolved during the procedure.

Control of Materials

Construction and characterisation of the parenteral *Saccharomyces cerevisiae* strain and the individual gene expression vectors were extensively described. For HPV types 6, 11, 16, and 18, plasmid or phage libraries were constructed from DNA obtained from human clinical specimens or cell lines positive for each targeted HPV type. In contrast, a similar breadth of research experience does not exist for the less-prevalent, less-studied HPV types 31, 33, 45, 52 and 58. Thus, the L1 gene for three or four clinical isolates was sequenced for each of these five HPV types. The natural sequence which was the most prevalent (dominant) was chosen. The design and features of the galactose-inducible expression system (with host cells), is the same for all types also including the approved types in Gardasil. The subsequent establishment of master and working cell banks (MCBs and WCBs) was described in detail. Sufficiently detailed information was provided on the analyses performed to confirm host strain identity and genetic stability of the individual L1 genes throughout production and on the

manufacture and control of master and working cell banks. Procedures for establishing future WCBs has been well described but for this application, based on previous experience with approved types, the applicant has proposed to delete a test for strain identity. This has been considered acceptable given the supportive data submitted.

A comprehensive list of all materials used in the manufacture of the individual MBAP products has been provided and the applicant has also clarified the nature and composition of MCB and WCB storage containers. In conclusion, the quality of materials used in production has been sufficiently described.

Process Validation

Process validation studies were well designed and cover all aspects of manufacture of the individual MBAP drug substances as well as the transport between the manufacturing sites and demonstrate that the process is capable of producing drug substance of consistent quality. The justification given to use a matrix approach for the validation studies is accepted. Reuse of filters and columns has been investigated. The control strategy applied for the various validation studies is considered adequate.

Characterisation

The format of characterisation studies performed on the new types follows, to a large extent, the format performed for the types included in the approved 4-valent vaccine Gardasil, with some variations to the types of methods applied. The applicant was therefore requested to explain and justify these differences and has done so appropriately. Overall, the experimental approach as implemented by the applicant, allows for a comprehensive experimental analysis and characterisation of DS (intermediate) materials addressing a large array of physico-chemical and functional parameters (structural elucidations of primary, secondary, tertiary, and quaternary structures including particle sizes; epitope integrity; antigenicity, immunogenicity, and completeness of adsorption). These data, gathered by a multitude of different experimental approaches are considered appropriate for the accurate characterisation of crucial quality attributes.

The protein sequence of all HPV types has been confirmed by MS. For most aspects on primary structure, the L1 proteins demonstrate heterogeneic features similar to the approved types, including N-terminal methionine truncation (31, 45, 52 and 58), N-terminal acetylation (78-100 %) in all types and partial removal of the last one or two C-terminal residues as determined from peptide mapping. Deamidation can occur at one to six sites and it is likely that less than or equal to 6% of L1 protein molecules in a FAP sample would be deamidated at one or more sites. Mass measurement studies on intact L1 proteins revealed significant amounts of a modification consistent with phosphorylation. According to references, phosphorylation of L1 has been shown to occur in native virions and recombinant produced L1. The applicant was asked to discuss the relevance of this modification in relation to clinical experience from approved HPV L1 types and the response cites previous experience and consistency with respect to phosphorylation. SDS PAGE analysis of intact monomer revealed, to a minor extent, a predominant clipping of all L1 types into 10 kDa and 45 or 47 kDa (depending on type) fragments, which is consistent with the approved L1 types. Clipping of L1 is controlled in the specification of % intact monomer.

Structural characterisation has been accomplished using Differential Scanning Calorimetry (DCS), Dynamic Light Scattering (DLS) and Transmission Electron Microscopy (TEM). Using TEM, tubular forms of VLPs can be detected. The applicant was asked to address the clinical experience with tubular VLPs in the approved types. Until now, no tubular forms were found in the old types. A need for routine monitoring of these by TEM was not considered necessary as these are subject to sufficient routine control of VLP structure by DLS testing and In vitro relative potency (IVRP) also these tubular forms were included in batches of the new types used in the clinical studies. DLS data showed some variability in polydispersity index, suggesting a higher variability in

particle size distribution compared to historic data from the approved types, still within the acceptance criteria for this index. The applicant has however shown that the increase has no impact on product quality to an acceptable extent. In addition, the calculations leading to this index were not originally described. The applicant has now submitted the relevant information.

Critical conformational epitopes on the VLP surface are the surrogate markers for VLP biological function, particularly with respect to the ability to induce a neutralising antibody response in animals and humans. It has been demonstrated that conformational epitopes on HPV Types 31, 33, 45, 52, and 58 can induce HPV type specific neutralisation. Therefore, characterisation of these epitopes is a central component for evaluation of structural integrity. Studies have been performed to investigate relative antigenicity using a panel of antibodies (per type) encompassing specificity towards conformational and linear epitopes. These results demonstrate an improved exposure of conformational epitopes when going from hydroxyapatite product to FAP, concomitant to a decrease in reactivity to hidden linear epitopes. Affinity, as shown by solution dissociation constant studies, does not change when going from hydroxyapatite product (HAP) to FAP.

The in vitro relative potency (IVRP) method is an important method to determine structural changes in the VLPs. In the previous application, data were included to demonstrate correlation of this method with in vivo potency determinations. The concept of the IVRP method is the same as for the approved product for which the suitability of the method with respect to estimation of immunogenicity of the batches has been sufficiently established by historical data and the feasibility of the method in this respect is confirmed by clinical data from this application. The capacity of the IVRP to detect storage related changes is demonstrated in the drug product section where a decrease in IVRP activity is detected upon incubation at elevated temperatures.

Data from extensive characterisation studies have also been applied to examine the comparability of alternative novel facilities used for fermentation of selected novel HPV types. In this context it is important to note that these new facilities have all received formal regulatory approval for the manufacture of the existing HPV types. For the original data provided for HPV type 31, 45, 52, 58 drug substance materials fermented in different buildings (B60 at West point and B63 at Stonewall), questions regarding comparability have been adequately resolved by the applicant.

Impurities

The extent of characterised product and process related impurities are similar to that of the approved types and have been clinically qualified. An overview of host-cell-derived impurities and process residuals (non-L1 protein, DNA, RNA, total lipid, total carbohydrates, antifoam, benzonase, RNase T1, pepstatin A, DTT, EDTA, citrate, phosphate) along with the assays used to monitor their concentrations has been provided. The following issues were identified. For type 31 produced at B60 an additional, HPV related, 60 kDa band was detected using western blot while no western blot studies of cell slurry from B63 was performed and the applicant was asked to justify the comparability in this respect. This form will be detected by the SDS-PAGE analyses and as mentioned below the acceptance criteria for this test (percent intact L1 monomer) has been further qualified. Furthermore, according to data provided on the removal of citrate, it appeared that this is not consistently removed during purification as one batch was out of trend and a clarification was requested. The applicant clarified that the level of this batch is still within clinically qualified limits and that it will continue to monitor citrate for up to three lots of type 31 within the application procedure to establish consistency, which is accepted.

Issues were identified regarding the definition of protein impurities. These are considered as active DS and not as impurities by the applicant. The applicant has justified this approach, and shown that both the HCP content and the extent of L1-protein fragmentation in DS batches are adequately controlled.

Regarding demonstration of clearance of yeast protein impurities, a minor point regarding the polyclonal serum was raised and has been appropriately resolved.

Specification

The applicant has provided a satisfactorily extensive data package on the control of the drug substance. DS release tests include protein concentration (bicinchoninic acid assay), percent purity (SDS-PAGE), percent intact monomer (SDS-PAGE), IVRP (three methods are specified but 'manual OD' and 'NIMBUS' methods will be used for release and stability of specified types), identity (as for IVRP), sterility (Ph.Eur.), endotoxin (Ph.Eur.), aluminium content (spectrometry), pH, characteristics (visual), and completeness of adsorption (as for IVRP). This testing programme is considered appropriate as it is equivalent to the already approved testing scheme for Gardasil. For the 9-valent vaccine, modified assay formats have been developed for IVRP testing. Apart from this, experimental methods have been adequately described and validated following a reasonable and sound validation strategy.

For the "old" HPV types a large batch database is available. This includes batch analysis data of clinical and process validation lots and data from three lots of each of the new types produced at commercial scale have also been submitted. Much less data have so far been collected for DS batches of the novel HPV types. Nevertheless, also for the novel HPV types, data from three batches per type have been submitted. The existing batch analysis data do not exhibit any unwanted trends or deviations that might cause a risk for drug substance quality.

Specifications for the "old" HPV types are either the same as approved during licensure of the 4-valent vaccine or have been slightly re-adjusted (tightened) by the applicant in line with available batch analysis data. Specifications for the novel HPV type DS have been implemented on the basis of a rather limited set of batch analytical data available to date. Proposed acceptance criteria for the two attributes Percent Purity and Percent Intact Monomer were requested to be aligned to levels found in product used in clinical trials since these attributes are important for efficacy and safety. The applicant has in his response submitted updated acceptance criteria and data to support that these may be considered clinically qualified. With this, the specifications are considered acceptable based upon the data currently available but should be reassessed as soon as batch analysis data from 20 batches of each type are available. The applicant has provided an acceptable program as to how this will be done (indicating those specifications which will be re-evaluated and justifying those that will not).

A description of the criteria and procedures for renewal of the primary standards, including the use of any correction factors, was lacking in the dossier. In its response, the applicant verified that the stability of the primary standard is monitored, that no downward trend has yet been seen and that the current standard is still considered acceptable. However, no description of any procedure for renewal of the primary standard (i.e., how the new standard will be qualified, including assigning its potency value and any calibration against the old standard) is provided. Thus, in the case that a new primary standard needs to be established, this will be the subject of a type II variation and the applicant has acknowledged that this is understood and will be followed.

Container closure

The description and characterisation of containers used for DS (intermediates) was largely considered satisfactory in the initial assessment. Upon request, the applicant has made reference to the specific Ph. Eur. requirements that have been taken into consideration for the selection and testing of the containers.

Stability

A very intensive stability assessment has been conducted. For the types included in the already licensed vaccine Gardasil (types 6, 11, 16, 18), a very broad database is currently available to support the claimed storage

periods for these types: cell slurry and MBAP. Stability has been assessed by analysis of a suitable panel of stability-indicating parameters and under normal (2-8°C), accelerated (23-27°C), and stressed (35-39°C) conditions.

The same testing scheme has also been used for the novel HPV types (31, 33, 45, 52, 58). Some of the studies are currently ongoing but the available data confirm DS stability and support the claimed storage periods for these new types: 60 months at -70°C (for cell slurry) and 36 months at 2-8°C (for MBAP).

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The complete drug product composition is presented in Table 1. The 9-valent HPV vaccine may be packaged in vials (type I glass Ph.Eur., elastomer stopper Ph.Eur. and flip-off cap), or prefilled syringes (luer-lock tip type I glass Ph.Eur. barrel with laminated stopper Ph.Eur.).

Table 1. Complete Drug Product Composition

Component	Quantity per 0.5-mL Dose	Function	Quality Standard
HPV Type 6 L1 Protein	30 µg	Immunogen	Internal specification
HPV Type 11 L1 Protein	40 µg	Immunogen	Internal specification
HPV Type 16 L1 Protein	60 µg	Immunogen	Internal specification
HPV Type 18 L1 Protein	40 µg	Immunogen	Internal specification
HPV Type 31 L1 Protein	20 µg	Immunogen	Internal specification
HPV Type 33 L1 Protein	20 µg	Immunogen	Internal specification
HPV Type 45 L1 Protein	20 µg	Immunogen	Internal specification
HPV Type 52 L1 Protein	20 µg	Immunogen	Internal specification
HPV Type 58 L1 Protein	20 µg	Immunogen	Internal specification
Amorphous aluminium hydroxyphosphate sulfate adjuvant	500 µg (aluminium content)	Adjuvant	Internal specification
Sodium Chloride	9.56 mg	Stabiliser	Meets USP and Ph. Eur.
L-Histidine	0.78 mg	Buffer	Meets Ph. Eur. (no USP monograph)
Polysorbate 80	50 µg	Stabiliser	Meets NF and Ph. Eur.
Sodium Borate [a]	35 µg	Buffer	Meets NF and Ph. Eur.
Water for Injection	QS	Solvent	Meets USP and Ph. Eur.

- USP: United States Pharmacopeia, Ph. Eur.: European Pharmacopoeia, NF: National Formulary
- [a] Listed in Ph. Eur. as borax

The composition is based on the currently licensed Gardasil vaccine. Excipients include: sodium chloride (to ensure stability), L-histidine (buffering agent for adsorption and final vaccine), and polysorbate-80 (stability of the VLP aqueous bulk and MBAP preventing surface adsorption and aggregation) and sodium borate (maintenance of a stable pH of the adjuvant during storage). The amorphous aluminium hydroxyphosphate sulfate adjuvant is used to enhance the immunogenicity of the HPV VLP vaccine. Higher quantities of aluminium adjuvant are used in Gardasil 9 than in Gardasil however this has been justified and supported by the safety profile. All excipients are controlled according to Ph. Eur.

Nonclinical and clinical dose-ranging studies were conducted to define the optimal target dose of each HPV virus-like particle type. Based on the results of these studies, the target protein concentrations selected in the

drug product were 60 µg/mL, 80 µg/mL, 120 µg/mL, 80 µg/mL, 40 µg/mL, 40 µg/mL, 40 µg/mL, 40 µg/mL, and 40 µg/mL for HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58, respectively. The aluminium content per dose for the 9vHPV Vaccine (500 µg) is greater than for the 4-valent HPV vaccine formulation (225 µg). Previous clinical experience with an 8-valent formulation containing HPV Types 6, 11, 16, 18, 31, 45, 52, and 58 and 225 µg aluminium indicated that addition of new HPV types to the 4-valent HPV vaccine formulation may result in somewhat lower anti-HPV titres for HPV Types 6, 11, 16, and 18. In an effort to keep the immunogenic response for HPV Types 6, 11, 16, and 18 non-inferior to that induced by the 4-valent HPV vaccine, the adjuvant content was increased to 500 µg aluminium per dose.

Regarding the container-closure system, suitability has been demonstrated by compendial testing of the components, leachable and extractable studies and drug product stability. Although Gardasil 9 vaccine in syringe lots has not been used in clinical studies, the syringes are made from the same glass as the vials. Integrity of the vial and syringe has been demonstrated (dye challenge test and aerobiology microbial challenge).

Manufacture of the product and process controls

Manufacture

All manufacturing operations (including previous clinical supply manufacture) and quality control testing of the vaccine are performed by Merck & Co., Inc., Sumneytown Pike, P.O. Box 4, West Point, Pennsylvania 19486-0004, USA. Commercial supply manufacture will occur at the same site. The most significant difference between the lab, pilot and commercial formulation processes is the incorporation of automated control systems in the production facility for some process steps.

Secondary packaging for both vials and syringes is performed by Merck Sharp & Dohme BV, Waarderweg 39, BN Haarlem. This site is also responsible for testing on importation and EU batch release.

The manufacturing process for the 9-valent Final Container Product (9vFC) in vials or syringes consists of two main steps: formulation and filling. The formulation is based on certain volumes of the components, but the actual transfer is monitored by weight. Critical process controls for these steps are provided. The formulated 9-valent Bulk Adsorbed Product (NBAP) is prepared from eleven sterile ingredients. At first, histidine buffer (0.5 M sodium chloride in 20 mM histidine buffer) and 2X alum in saline with polysorbate 80 (PS-80) are mixed into a portable tank for formulation. The Type 6, 11, 16, 18, 31, 33, 45, 52 and 58 MBAPs are then sequentially added to the same tank. A settle and subsequent decant step has been introduced to achieve the final formulation concentrations for aluminium and potency for each HPV type. For the settling time, a design space was established taking into consideration the temperature and starting aluminium concentrations. Upon blending, each type-specific protein concentration is reduced from 320 µg/ml to the target concentrations selected in the drug product which were 60 µg/mL for HPV type 6, 80 µg/mL for HPV type 11, 120 µg/mL for type 16, 80 µg/mL type 18, 40 µg/mL for type -31, 40 µg/mL for type 33, 40 µg/mL for type 45, 40 µg/mL for type 52, and 40 µg/mL for type 58. Following completion of the decant process, the Final Formulated Bulk (FFB) is mixed to ensure homogeneity, aseptically sampled for testing of sterility and aluminium concentration and finally cooled to 2-8 ºC before filling or storage. Before and during filling, the FFB is agitated and recirculated to ensure homogeneity. The formulation process allows for multiple options for FFB storage. The target batch size for the FFB is approximately 315 kg.

Aseptic filling and stoppering of the 9vFC vaccine in vials occurs in the barrier isolator system. Before filling, homogeneity is ensured by mixing the FFB in the portable tank by agitation and recirculation. The FFB is continuously agitated and recirculated throughout the fill. An automatic filling machine, equipped with sterile components, aseptically fills the FFB into vials such that each vial or syringe contains a minimum recoverable

volume of 0.5 ml. During filling, in-process weight checks are performed routinely. After each vial or syringe is filled, it exits the isolator and is inspected for defects. Quality control samples are taken during the fill. After inspection, the vials and syringes are placed into trays and stored at 2-8 ºC until they are labelled and packaged. Process validation studies for formulation, vial filling and syringe filling for the 9vHPV vaccine were performed. The purpose of these studies was to qualify the formulation, vial and syringe filling processes for the 9vHPV Vaccine. The process validation of formulation and vial filling consisted of four consecutive lots of the 9vHPV Vaccine formulation as well as vial filling processes and the syringe filling validation consisted of three consecutive lots of the 9vHPV Vaccine syringe filling process. One of the batches to be filled in vials was filled at or close to the maximum batch size of 315 kg while two syringe batches were filled at this scale.

The information provided in the dossier for manufacturing of Drug Product was not considered sufficient in the initial application. A significant part of validation data has been placed in the description of the manufacturing process development. As these studies serve to define the outer boundaries of the process as intended to be run for future batches, these parts were asked to be moved to the section on process validation instead. Additionally, a summary of real data was requested, not only statements. The applicant has updated the file in an acceptable way on these issues. In conclusion, the studies demonstrate the capability of the process to produce drug product of consistent quality.

The company originally claimed that since certain steps are well controlled, they are not critical and therefore not described in detail in the dossier. This was not accepted. The fact that it is well controlled only lowers the risk but since the criticality classification is based on the testing performed, a description of how changes to this testing (methods, limits) will be handled to assure a sufficient regulatory oversight was requested. The applicant has responded to this and it has been clarified that the EU regulation on variations will be followed when evaluating changes to Drug Product, Critical Process Parameters (CPPs), Key Operating Parameters (KOPs) and analytical methods, and a variation will be submitted as required in accordance with the regulation.

The data to support the statement that 30 minutes of resuspension ensures a robust resuspension for bulk input resuspension, pre-settle resuspension, or FFB resuspension and sampling step during the entire shelf lives of the components was requested and acceptable data have been provided and the description updated. For the settling operation, a design space is claimed built on aluminium concentration and temperature. Its establishment was requested to be described in more detail and justified and the design space requested to be included in the description of the process. The applicant has submitted an acceptable answer to this.

Product specification

The final product, as packaged in vials, is tested for in vitro relative potency (IVRP, same test as for DS). Identity (IVRP), sterility (Ph.Eur.), endotoxins (Ph.Eur.), aluminium (spectroscopy), pH (Ph.Eur.), characteristics and package identity (visual checks), recoverable volume (gravimetrical test) and syringeability (to ensure that liquid is dispensed from the needle in an even stream), which is performed on syringes only.

Batch analysis data for 18 FFB lots used to produce drug product at pilot and full manufacturing scales for clinical studies, stability studies, and process validation all fulfilled the requirements for sterility and aluminium.

For the drug product, all batches (n= 12 clinical lots, 24 other lots) fulfilled the specification and showed good reproducibility. The same pattern as regards aluminium was seen. The results of the IVRP analyses were consistent between batches and considerably higher than the lower specification limit. The acceptance criteria applied in the tests for identity, sterility, endotoxins, pH, characteristics, volume of fill and syringeability are non-controversial and can be accepted. In the initial assessment the specification of aluminium content appeared wide and was not supported by the batch data. The specification has been appropriately updated in this respect. During development, a test for completeness of adsorption and one for general safety was

performed but these are proposed to be deleted. Considering the results shown, the test for completeness of adsorption can be removed from the specification but this should be performed when assessing any potential changes to the final product manufacturing process and the applicant has agreed to do so. The removal of the general safety test is also endorsed.

The justification for the lower IVRP limits was not accepted as the applicant only based this on process capability and did not provide any supporting evidence that the lower level would be clinically justified, as the batch data submitted for clinical and other batches were in no cases near the lower limit.

The applicant was asked to revise the limits to assure that a clinically justified level can be assured throughout the entire shelf life of the product and set release limits taking any loss during storage into account. One aspect requested to be taken into account in the justification is if the clinical batches were assayed by the TECAN and not the NIMBUS assay. This issue constituted a major objection. In the response, the applicant elaborated on how the claimed lower efficacious doses were calculated. In contrast to Gardasil where actual serological studies were performed with fractions of the antigen doses, in Gardasil 9 there are no clinical data from lower doses of most of the types since the low dose batches contained the same amount of the new types as the mid dose presentation.

No actual justification on the use of 0.5 for the lower 95% confidence limit for the geometric mean ratio (2-fold non-inferiority margin) has been submitted in the applicant's response, but it is recognised that this has been used in many of the clinical studies and does therefore not raise any concerns. The principle to calculate the lowest effective dose based on the dose finding data can be accepted and it is acknowledged that the specifications claimed at release and during shelf life allow a safety margin compared to the claimed lowest clinically effective dose. For this reason the proposed specification can be accepted.

The reference standard used for routine testing is a 9-valent Final Container Product (9vFC) lot, which is referred to as the working standard. The same standard is used for both IVRP and completeness of adsorption (i.e. use of the IVRP assay to measure the amount of HPV VLP in a vaccine sample that is not adsorbed to the aluminium adjuvant). The current lot of working standard, is a clinical manufacturing lot that was formulated and filled at pilot scale using MBAPs manufactured at full scale. An acceptable protocol for qualification of new working standards has been provided.

Stability of the product

For the final formulated bulk, 12 month data from 3 lots produced at pilot scale and 3 lots produced at full scale are presented, tested at 2-8°C, 23-27°C and 35-39°C. The proposed shelf life for the two container types (syringes and vials) is 36 months at 2-8°C, with TOR allowances of 10 days at 25°C and one day at 37°C. However, in order to minimise the risk of uncontrolled product storage and subsequent deterioration, only TOR allowances of 72 hours (when stored at temperatures from 8°C to 25°C or from 0°C to 2°C) have been approved in the product information, with the instruction to use or discard the product at the end of this period.

For vials, 42 months data from three pilot scale batches are presented and 36 months data from four full scale batches, at 2-8 °C. Respective data from samples stored at 23-27°C and 35-39°C are also available.

For the commercial syringe presentation (image 5), data for up to 30 months are available from 1 full scale batch and 2 pilot scale batches stored at 2-8°C and 1 full scale batch and 1 pilot scale batch stored for 6 months at 35-39°C. Further data are available from syringes (image 1) fully comparable to the commercial presentation except for a different tip cap for which the differences are considered to have negligible potential impact and therefore can be considered fully representative for the commercial product. Here, data are available from 3 pilot scale and 4 full scale batches stored for at least 36 months at 2-8°C, for up to 24 months at 23-27°C, and

for 6 months at 35-39°C. In addition, supportive data are provided from 3 other packaging material variants (image 2-4) produced at pilot scale. All test attributes in the release specifications are included in the stability studies, except IVRP upper limits, identity, endotoxin, aluminium, package identity and volume of fill. In addition to the release specifications, test for completeness of adsorption (IVRP) are included in the stability studies.

No significant changes in physical appearance, completeness of adsorption, pH, or sterility can be observed in the available data from 2-8°C. To estimate the loss rate for the IVRP, a statistical analysis was performed via linear regression of log transformed data, using a random slope, fixed intercept mixed model. Stability data from 2-8°C, 23-27°C and 35-39°C of at least 3 months were included. The stability data from both containers and the final formulated bulk were combined for the statistical evaluation of loss estimated for each subtype, because the sample matrices between the final formulated bulk and the two types of container are equivalent. The only exception was HPV type 11 at 2-8°C and HPV types 18 and 52 stored at 35-39°. These data did not fulfil the statistical criteria for pooling and only the FFB data were used for the loss rate estimate. Stability for all subtypes was shown when stored at 2-8°C, with higher losses at 23-27°C and 35-39°C, as expected. No clear trends are evident and the observed fluctuations are attributable to the assay variation.

In addition to the stability studies, a thermal stress study on one vial lot and one syringe lot was conducted. This study is completed and the results support the expiry specification, TOR exposures and product shipping and handling. Moreover, a sequential stability study has been initiated to evaluate the cumulative effect of multiple holds during routine storage of MBAP, FFB, and 9vHVP vaccine. This study is ongoing. Furthermore, a photostability study with 9vHPV vaccine was performed where HPV Type 18 was shown to be somewhat sensitive to UV light, but to an acceptable range.

In summary, the results support the final formulated bulk (FFB) storage period and 9vHPV vaccine expiry, as well as respective TOR exposure periods. Initially the decision on the final shelf lives awaited the outcome of the major objection on justification of acceptance criteria. Since the claimed IVRP specifications now can be accepted this means also that the claimed shelf life of 12 months in 2-8 °C for the final formulated bulk and 36 months for the final product under the same conditions can be accepted.

Adventitious agents

Two raw materials used in the working cell bank and fermentation processes, D-galactose, and L-Tyrosine, were identified to be of direct human or animal origin. D-Galactose is derived from bovine milk sourced from the United States; the milk is sourced from healthy animals in the same manner as milk for human consumption. This material was determined to be compliant with the EMA Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (EMA/410/01 Rev 3, July 2011). L-tyrosine is extracted from human hair sourced from China or from poultry feathers. Regarding the TSE status of this raw material, amino acids from human hair are prepared using harsh conditions and therefore, according to the TSE guideline, they are unlikely to present any TSE risk and are considered to be compliant with the guideline. The provided documentation regarding viral safety is deemed sufficient.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Drug substance

The manufacturing and controls for the 4-valent HPV Types in Gardasil 9 are the same as the manufacturing and controls for the 4-valent HPV Types currently licensed and approved for Gardasil/Silgard, with some exceptions. The process is well defined and was extensively characterised and acceptably validated.

For the HPV types 6, 11, 16, 18 included in the licensed 4-valent vaccine "Gardasil" drug substances (MBAP) and intermediates (hydroxyapatite product and FAP) have been tested according to the previously established and approved comprehensive programme. Basically, the same testing scheme has been applied for the novel HPV types 31, 33, 45, 52, 58 to be included for the formulation of the 9-valent vaccine. Certain distinct changes in methodologies have been acceptably justified and the applicant has provided the scientific rationale and reason(s) for these technical alterations. The applicant has also clarified certain findings from the characterisation studies of new L1 types in relation to clinical experience of the existing L1 types, including the relevance of L1 phosphorylation and relevance of variability in polydispersity index of tubular VLPs which had suggested a higher variability in particle size distribution.

The applicant has verified that the DLS method, including the calculation of polydispersity index (PDI), and the acceptance criteria for hydrodynamic diameter (Dh) and PDI proposed for Types 6, 11, 16 and 18, is the same as approved for Gardasil. In addition, an update of the MAA file containing a description of the DLS test, including how the PDI is calculated, and the acceptance criteria, has been submitted.

Data from these extensive characterisation studies have also been applied to examine the comparability of alternative novel facilities used for fermentation of selected novel HPV types. Some specific questions regarding the comparability of material produced in the different buildings have now been resolved.

Characterisation and clearance studies for impurities have been performed mainly on the basis of the operations already in place for the approved 4-valent vaccine which is considered appropriate. Results confirm that levels of (defined) impurities are acceptably low and under proper control.

The drug substance specifications are acceptable. The proposed acceptance criteria for the two attributes Percent Purity and Percent Intact Monomer, was considered to be wider than what has been shown to be safe and efficacious in clinical trials. The applicant has now submitted revised acceptance criteria as well as acceptable clinical justification of the proposed limits. Since specifications for the novel HPV type DS (types 31, 33, 45, 52 and 58) have been implemented on the basis of the rather limited set of batch analytical data available to date, the applicant was asked to reassess the specifications for all new types when sufficient data become available. In its response, the applicant has agreed to re-evaluation of certain acceptance criteria (percent purity, percent intact monomer and IVRP), justifying that other DS specifications will not change with additional batch data The re-evaluation will be performed following availability of data from 20 batches of each type according to an agreed protocol. This has been accepted and is included as a recommendation.

Drug product

The information provided in the dossier for manufacturing of Drug Product was not originally considered sufficient. A significant part of validation data was placed in the description of the manufacturing process development and has now been moved.

The company claimed that since certain steps are well controlled, they are not critical and therefore not described in detail in the dossier. The applicant was asked how changes to this testing (methods, limits) will be handled to assure sufficient regulatory oversight and the applicant has provided satisfactory clarification regarding this. In relation to the final DP specifications, the justification for the lower IVRP limits have been expanded to explain how the limits can be considered as clinically qualified in an acceptable way and the major objection is thereby resolved. Final assignment of shelf lives for the formulated final bulk and the drug product awaited the outcome of this question and as it has now been resolved, the claimed shelf lives can as a consequence be approved.

For some issues although acceptable responses have been submitted, the file remains to be updated and the applicant has committed to do so.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety. Two recommendations for future quality development of the product is listed below.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

Area	Number	Description	Classification
Quality	001	DS acceptance criteria for Percent Purity, Percent Intact Monomer will be reassessed for types 31, 33, 45, 52 and 58 according to the statistical methods (as described in the Day 181 Responses as soon as batch analysis data from at least 20 batches of each type are available.	REC
Quality	002	DS acceptance criteria for IVRP will be reassessed when batch analysis data from at least 20 batches of each type are available. The DS reassessment will be planned as part of an overall IVRP acceptance criteria reassessment, which will be performed when sufficient release and stability data for both DS and DP can be integrated into the original dataset.	REC

Non-clinical aspects

2.2.7. Introduction

The pharmacological evaluation of GARDASIL 9 was focused on the evaluation of immunogenicity. One non-GLP immunogenicity study was performed in non-human primates (Rhesus macaques) to determine whether an HPV VLP-specific immune response was elicited by the vaccine.

The nonclinical toxicology of Gardasil 9 was evaluated in 3 studies, all carried out under GLP-compliant conditions. They include an intramuscular repeat-dose toxicity study in rats (with local tolerance and non-GLP immunogenicity assessments), an intramuscular developmental toxicity and immunogenicity study in rats with fertility and embryo-foetal evaluation, and an intramuscular developmental toxicity and immunogenicity study in rats with postnatal evaluation.

All non-clinical toxicity studies were conducted in compliance with the GLP, which is in line with the current requirements.

2.2.8. Pharmacology

The pharmacological evaluation of the 9vHPV vaccine was focused on the evaluation of primary pharmacodynamics (i.e. immunogenicity) as the vaccine did not show any effects apart from the expected immune response. This is consistent with the CHMP Note for Guidance on Preclinical Pharmacological and Toxicological Testing of Vaccines and with the WHO Guidelines on Nonclinical Evaluation of Vaccines.

Primary pharmacodynamic studies

There is no animal model for human papilloma virus infection. Therefore, the vaccine could not be tested for protection in animals. The pharmacology studies are focused on the evaluation of immunogenicity.

To support the development of Gardasil 9, the applicant performed an immunogenicity study in Rhesus macaques (study PD001).

Methodology

One group of six Rhesus macaques (2 females, 4 males, 6-8 years of age) received three 0.5 mL intramuscular injection in right deltoid muscle with 9vHPV vaccine on Day 0, Week 8 and Week 24. Formulation of 9vHPV vaccine consisted of 2 µg/4µg/4µg/2µg/2µg/2µg/2µg/2µg/2µg of HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58 VLPs per 0.5 mL dose, and 309.5µg AAHS per 0.5 mL dose.

Immunogenicity was assessed by competitive Luminex Immunoassay (cLIA) (8-plex cLIA) for the following 8 HPV types: 6, 11, 16, 18, 31, 45, 52 and 58. Immunogenicity for type 33 was determined by serial end-point dilution in a HPV 33 VLP direct binding ELISA. The study evaluated the antibody response to HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58 L1 VLPs formulated with AAHS.

Results

Intramuscular administration of 3 doses of the nine-valent HPV L1 VLP vaccine formulated with AAHS was well tolerated in Rhesus macaque monkeys. The vaccine elicited a robust immune response in all the animals resulting in the production of antibodies against each of the nine HPV types (6, 11, 16, 18, 31, 33, 45, 52 and 58) present in the vaccine. This study demonstrates the immunogenicity of all 9 monovalent HPV L1 VLPs (6, 11, 16, 18, 31, 33, 45, 52 and 58) as a nine-valent formulated vaccine in non-human primates. These data support the hypothesis that 9-valent HPV L1 VLP vaccine will elicit HPV protection from infection through humoral immunity in human clinical trials.

In conclusion, intramuscular administration of the 9vHPV vaccine was well tolerated and immunogenic in Rhesus macaques.

Secondary pharmacodynamic studies

Secondary pharmacodynamics studies were not performed for the 9vHPV vaccine, since the vaccine did not show any effects apart from the expected immune response. This was found acceptable by the CHMP under the current requirements.

Safety pharmacology programme

Safety pharmacology studies were not performed for the 9vHPV vaccine. This is in accordance with the WHO Guidelines on the Nonclinical Evaluation of Vaccines, which suggests that safety pharmacology tests for vaccines should be performed only if data from nonclinical and/or human clinical studies suggest that the vaccine may affect physiological functions (central nervous system (CNS), respiratory, cardiovascular, and renal functions) other than the immune system. The 9vHPV vaccine has been tested in nonclinical safety assessment studies

where daily monitoring for physical signs did not reveal any notable effects on any physiological function. In addition, the safety of the 9vHPV vaccine has been tested in human clinical studies and no signs of concern have been identified. Apart from the expected immune response and local injection site reactions, there has not been any evidence of systemic effects (such as effects on CNS, respiratory, cardiovascular, and renal systems) caused by HPV L1 VLP vaccines.

Therefore, given that there were no signs of CNS, respiratory, cardiovascular and renal effects for the 9vHPV vaccine, a nonclinical safety pharmacology study was deemed to be not necessary for the 9vHPV vaccine. This was found acceptable by the CHMP under the current requirements.

Pharmacodynamic drug interactions

Pharmacodynamics studies were not performed for the 9vHPV vaccine. The potential interference with other vaccines is an important aspect, but can only be addressed in clinical studies.

2.2.9. Pharmacokinetics

No studies on absorption, distribution, metabolism or excretion were performed. This is in line with the CHMP Note for Guidance on Preclinical Pharmacological and Toxicological Testing of Vaccines and is therefore acceptable.

2.2.10. Toxicology

Toxicology studies supporting the safety of the 9vHPV vaccine included 3 GLP-compliant studies in rats consisting of: i) a repeat-dose toxicity study (with local tolerance and non-GLP immunogenicity assessments), ii) an intramuscular developmental toxicity and immunogenicity study with female fertility and embryo-foetal evaluation and iii) an intramuscular developmental toxicity and immunogenicity study with postnatal evaluation. The only treatment-related effects were indicative of the immune response and injection site reactions.

These studies provide an extensive evaluation of the preclinical safety of the 9vHPV vaccine and support the administration of this vaccine to humans.

The 9vHPV vaccine contains the four HPV VLP types that are present in the quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine, in addition to five new HPV L1 VLP types (31, 33, 45, 52, and 58). It should be noted that the nonclinical toxicology of the quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine has been previously assessed. Of much more importance for the safety assessment is the large safety database available for the 4-valent vaccine (Gardasil). Based on the similarities between the vaccines, no important difference in safety is anticipated.

Toxicology studies of AAHS alone were not performed because this adjuvant has been used before in several other Merck vaccines and has an established safety profile.

Single dose toxicity

Single-dose toxicity was assessed within a repeat-dose toxicity study, which is acceptable.

Repeat dose toxicity

A three-month intramuscular toxicity GLP-compliant study was performed in rats dosed once every 21 days with a 21-day recovery period. The objective of the study was to determine the potential toxicity and immunogenicity of the 9-valent HPV Vaccine, formulated in Merck Aluminum Adjuvant (MAA), when administered intramuscularly to rats once on each of Study Days 1, 22, 43, and 64.

No treatment-related deaths were noted. Treatment-related antemortem findings were limited to very slight to moderate changes in hematological parameters and biochemical parameters observed in females and males at all doses (low-dose, mid-dose, high-dose), such as increases in leukocytes, neutrophil, eosinophil, and monocyte counts on Study Day 67 only, and decreases in albumin values and increases in globulin. These are anticipated immunological responses, which were recovered or at least partially recovered by the end of the 21-day recovery period. These changes were likely attributed to non-specific immune responses, and could be expected for a vaccine.

At interim necropsy (3 days after the last dose) but not at final necropsy (after a 21-day recovery period), statistically significant increases in splenic weights, with no gross or histomorphologic correlate, were observed in female rats injected with the mid- and high-dose of the vaccine. The increase in splenic weights was considered an expected secondary effect to the stimulation of the immune system by vaccination and was converted to normal range following a 21-day recovery. Theoretically, immune stimulation holds a risk of causing/exacerbating autoimmune diseases, but such a risk can only be characterized in post-marketing settings.

Histopathological findings were observed at injection sites and in draining lymph nodes, which is expected for a vaccine containing Alum, and the effect appears to be mainly caused by the adjuvant. Given a total amount of 500 µg Alum within the 9vHPV vaccine formulation (instead of 225 µg in GARDASIL), a 21-day recovery period appears not sufficiently long to allow detection of fully or partial recovery of the effect when evaluated by muscle inflammation and lymph node hyperplasia. Nonetheless, absence of myofiber degeneration and reduced severity of inflammation at the end of recovery suggest ongoing resolution of the skeletal muscle changes.

For immunogenicity evaluation, the 9vHPV vaccine induced humoral immune responses against all 9 HPV serotypes (HPV Type 6, -11, -16, -18, -33, -31, -45, -52, and -58) following one or four intramuscular injections to rats at all dose levels, as a pharmacological effect. In contrast, there was generally no detectable antibody response against any of these HPV serotypes in the PBS or adjuvant control groups at any time point, as expected.

Genotoxicity

The *in vitro* and *in vivo* genetic toxicity/mutagenic potential of the 9vHPV vaccine were not evaluated. According to the CHMP Note for Guidance on Preclinical Pharmacological and Toxicological Testing of Vaccines, the WHO Guidelines on Nonclinical Evaluation of Vaccines and the Japan's Ministry of Health, Labor and Welfare "Guideline for Non-clinical Studies of Vaccines for Preventing Infectious Diseases", genotoxicity studies are not generally required for vaccines. The CHMP agreed.

Carcinogenicity

The oncogenic/carcinogenic potential of the 9vHPV vaccine in long and short-term studies was not evaluated. According to current requirements as mentioned above, carcinogenicity studies are generally not required for vaccines and this is acceptable also for Gardasil 9.

Reproduction Toxicity

The reproductive and developmental toxicity of the 9vHPV vaccine was assessed in two GLP-compliant studies using female rats. The reproductive and developmental toxicity evaluation is an important part of the overall safety assessment for this vaccine because the 9vHPV vaccine is indicated for use in women of childbearing potential. The study designs were developed with reference to CBER/FDA's Guidance for Industry on "Considerations for Developmental Toxicity Studies for Preventive and Therapeutic Vaccines for Infectious Disease Indications" and previous experience with another HPV L1 VLP vaccine, which was found acceptable.

The results of the study on embryo-foetal development show that three 0.5 mL (0.25 mL administered to each quadriceps muscle) intramuscular injections, at a dose of 30/40/80/55/30/30/30/30/30 µg HPV VLPs and 500 µg MAA adjuvant, given at 5 and 2 weeks prior to cohabitation and on GD 6, is not teratogenic, and is well-tolerated in female/pregnant rats and without adverse effect on female mating performance and fertility.

Concerning the study on intramuscular developmental toxicity and immunogenicity study in rats with postnatal evaluation, the results show that four 0.5 mL (0.25 mL administered to each quadriceps muscle) intramuscular doses of 9vHPV vaccine, administered to F0 females at 5 and 2 weeks prior to cohabitation, on Gestation Day (GD) 6 and on Lactation Day (LD) 7, did not cause adverse effects on development, growth, behaviour, reproductive performance, and fertility of the F1 generation in rats.

Local Tolerance

An assessment of local tolerance for the 9vHPV vaccine was included within the repeat-dose toxicity study in rats. The results demonstrated that the changes at the injection site were of minimal toxicological significance and within acceptable tolerability limits for intramuscular vaccine treatment in rats with AAHS-containing formulations.

Other toxicity studies

No other toxicity studies were performed, since no specialized toxicological assessments were needed for this vaccine. The CHMP agreed.

2.2.11. Ecotoxicity/environmental risk assessment

An environmental risk assessment has not been conducted. The vaccine consists of proteins and as such it is not considered to constitute a risk to the environment.

2.2.12. Discussion on non-clinical aspects

Non-clinical toxicological testing of the 9vHPV vaccine includes 3 GLP-compliant studies in Sprague-Dawley rats, consisting of a repeat-dose toxicity study (complete toxicity with local tolerance and non-GLP immunogenicity assessments), a female fertility and embryo-foetal developmental toxicity study, and a postnatal developmental toxicity study.

In the repeat-dose toxicity study, three dose levels (low-dose, mid-dose, high-dose) of the vaccine were assessed with the mid-dose level being similar to the final formulation to be licensed. Four 0.5-mL (0.25 mL/quadriceps) intramuscular dose administrations on study Days 1, 22, 43, and 64, followed by an observation period of approximately 3 weeks, showed a favourable safety profile. There were no treatment-related effects on mortality, physical signs, body weight, food consumption, ophthalmic, or urinalysis parameters. Treatment-related antemortem findings include changes in hematology and blood chemistry, such as very slight increases in white cell count, decrease in albumin values and increase in globulin, resulting in decreases in A/G ratio. These changes were consistent with the expected immunological response induced by the vaccine, and were transient. Treatment-related postmortem findings include transient increases in spleen weights with no gross or histomorphologic correlates, and histomorphologic findings at the injection site and in the draining lymph nodes, such as inflammation and transient muscle fibre degeneration observed in the quadriceps muscle, and hyperplasia of the draining iliac and inguinal lymph nodes correlated with the increased size of lymph nodes observed grossly. The change observed in the draining lymph nodes was of similar frequency and severity in adjuvant-placebo versus high-dose vaccine groups, and was considered secondary to stimulation of the immune

system by the adjuvant. Ongoing resolution of these changes was suggested by the absence of myofibre degeneration and the reduced severity of inflammation and hyperplasia at the end of a 21-day recovery.

Antibodies against each of the 9 HPV L1 VLP types were found in every 9vHPV vaccine-treated group.

In addition, two GLP-compliant studies on reproductive and developmental toxicity of the 9vHPV vaccine were conducted in female Sprague-Dawley rats.

In the first developmental toxicity study, female rats (F0) received three 0.5 mL (0.25 mL administered to each quadriceps muscle) intramuscular injections at 5 and 2 weeks prior to cohabitation and on Gestation Day (GD) 6. There were no treatment-related adverse effects in the F0 females, including mating performance and fertility. No treatment-related adverse effect on the embryo-foetal development of the F1 generation was observed after routine uterine and foetal examinations, which include assessment of numbers of corpora lutea, implantations, and live foetuses and embryonic/foetal viability, foetal weights, sex ratios, and external, visceral, coronal, and skeletal morphology. Transfer of antibodies specific against all 9 HPV serotypes from vaccine-treated dams to GD 21 foetuses was evidenced by immunogenicity data.

In the second developmental toxicity study, female rats (F0) received 0.5 mL (0.25 mL administered to each quadriceps muscle) intramuscular injection with 9vHPV vaccine on 4 occasions (Premating Week -5 and -2 plus GD 6 and LD 7). There were no vaccine-related effects in F0 females and no treatment-related adverse effects on development, growth, behaviour, reproductive performance, and fertility of the F1 generation in rats.

In conclusion, the non-clinical toxicity testing programme designed for the 9vHPV vaccine is adequate. The three to four intramuscular doses of vaccine were well tolerated in rats in all conducted toxicity studies. Theoretically, lymphoid stimulatory effect seen in repeat-dose toxicity study might cause/exacerbate autoimmune diseases, but such a risk can only be characterized in post-marketing setting in humans.

2.2.1. Conclusion on the non-clinical aspects

The immunogenicity study PD001 in non-human primates demonstrated immunogenicity against all 9 HPV types and supported the clinical development of the product.

There are no safety concerns identified from the 3 non-clinical toxicology studies performed for Gardasil 9.

Clinical aspects

2.2.2. Introduction

The demonstration of efficacy of the 9vHPV vaccine is based on comparison of its efficacy and immune responses results to qHPV. Efficacy can only be studied in women 16-26 years of age due to sexual naivety of the younger age group that is the main target for vaccination (9-15 years of age). In the age group 16-26 years of age, non-inferior immune responses to the 4 HPV types common to both vaccines were the main surrogate markers for efficacy. In addition, no negative trend in efficacy was demonstrated. For the 5 new HPV types, clinical efficacy was to be demonstrated in comparison to qHPV for the age group 16-26 years. In younger subjects, boys and girls 9-15 years of age, and in men 16-26 year of age, serological bridging to the efficacy population, i.e. women 16-26 years of age, and to qHPV recipients 9-15 years of age was considered acceptable as a surrogate measure of efficacy. This is in line with the clinical development for Gardasil, where efficacy was demonstrated in women 16-26 and serological bridging was considered acceptable to extrapolate efficacy to younger subjects. In addition, both vaccines have similar claims for protection, i.e. against the same disease endpoints, the only difference being the number of virus types included in the vaccine formulations.

In summary, the indication of Gardasil 9 is based on:

- non-inferior immunogenicity between Gardasil 9 and the qHPV vaccine for HPV Types 6, 11, 16 and 18 in girls and women 9 to 26 years of age; consequently, efficacy for Gardasil 9 against persistent infection and disease related to HPV Types 6, 11, 16, or 18 can be inferred to be comparable to that of the qHPV vaccine;
- demonstration of efficacy against persistent infection and disease related to HPV Types 31, 33, 45, 52 and 58 in girls and women 16 to 26 years of age, and
- demonstration of non-inferior immunogenicity against the Gardasil 9 HPV Types in boys and girls 9- to 15 years of age and men 16- to 26-years of age, compared to girls and women 16-to 26-years of age.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study Protocol	Study Design/Sites	Study vaccine/arm/No. of subjects	Population and age	Primary Endpoints	Duration and follow-up (FU)
P001 Phase IIb/III *Part A/Phase IIb*: ***Substudy*** 1) Dose- ranging *Part B/Phase III*: ***Substudies*** 2) Immunogenicity 3) Efficacy	Double-blind, randomized 105 centers: US (28) and Ex-US (77) incl. Austria, Brazil, Canada, Chile, Colombia, Denmark, Germany, Hong Kong, Japan, Mexico, New Zealand, Norway, Peru, Republic of Korea, Sweden, Taiwan, Thailand	9vHPV/qHPV *Part A* n=619/620 *Part B*, n= 7,099/7,105 for immunogenicity and efficacy 3 doses at Month 0, 2, 6	16-26 years-old females	*Part A:* - General tolerability - GMTs at 4 weeks post-dose 3 (4 *original* types) *Part B:* - General tolerability - GMTs at 4 weeks post-dose 3 (4 *original* HPV types) - Combined incidence of high-grade genital diseases and cancers related to 5 *new* types after median 30 months FU and at least 30 cases of high-grade disease	*Part A*: 7 months *Part B:* Immunogenicity: 42 months Efficacy: at least 42 months (up to FU 54 months)
P002 Phase III ***Substudies*** 1) Adolescent Bridging 2) Lot consistency	72 centers located throughout Africa, Asia-Pacific, Europe, Latin America, and North America Open-label, non-randomized Double-blind, randomized	9vHPV 3 vaccine lots n=3,066 3 doses at Month 0, 2, 6	9-15 years-old girls and boys, in a comparison with 16-26 years-old females	- General tolerability - GMTs at 4 weeks post-dose 3 (all 9 vaccine types)	12 months (FU 36 months)
P003 Phase III Safety Immunogenicity	Open label, randomized 76 centers: US (24) and Ex-US (52) incl. Canada, Colombia, Denmark, Germany, Israel, Malaysia Mexico, Norway, Peru, Philippines, Poland, South Africa, Spain, Sweden, Thailand, Turkey.	9vHPV 3 doses at Month 0, 2, 6 N=2500 1100 HM 1100 females 300 MSM	16-26 years old males and females	- GMTs at 4 weeks post-dose 3 - General tolerability	7 months immunogenicity 12 months safety
P005 Phase III Concomitant Menactra and Adacel	Open-label randomized 41 centers: US (34) and Ex-US (7) incl. Chile, Colombia, Mexico, Peru	9vHPV+ [Menactra+Adacel]/9vHPV n=619/618 9vHPV: 3 doses at Month 0, 2, 6 [Menactra+Adacel]: at Month 0 (concomitant) or Month 1 (non-concomitant)	11-15- year old girls and boys	- General tolerability - GMTs at 4 weeks post-dose 3 for 9vHPV vaccine antigens - SCR at 4 weeks post-dosing for MenA-C-Y-W135 antigens - SPR at 4 weeks post dosing for D, T antigens - GMTs at 4 weeks post dosing for pertussis antigens	7 months
P006 Phase III Tolerability and immunogenicity	Double-blind, randomized 32 centers: US (10), Ex-US (22) incl. Australia, Canada, Colombia, Denmark, Hong Kong, Mexico, Sweden	9vHPV/placebo n=615/306 3 doses at Month 0, 2, 6	12-26-year old females previously receiving Gardasil	- General tolerability - SCRs to each of *5 new* HPV vaccine types	7 months

P007 Phase III Concomitant Repevax	Open-label randomized 22 centers: Austria, Belgium, Denmark, Finland, Germany, Thailand	9vHPV+ [Repevax]/9vHPV n=525/528 9vHPV: 3 doses at Month 0, 2, 6 [Repevax]: at Month 0 (concomitant) or Month 1 (non-concomitant)	11-15- year old girls and boys	- General tolerability - GMTs at 4 weeks post-dose 3 for 9vHPV vaccine antigens - SPR at 4 weeks post dosing for D, T antigens - GMTs at 4 weeks post dosing for pertussis antigens - SPR at 4 weeks post dosing for poliovirus antigens	7 months
P009/GDS01C Phase III Immunogenicity and tolerability	Double-blind, randomized 24 centres: Belgium, Denmark, Finland, Italy, Spain, Sweden	9vHPV/qHPV n=300/300 3 doses at Month 0, 2, 6	9-15-year old girls	- GMTs at 4 weeks post-dose 3 (HPV-16, -18)	7 months

* = Mid-dose selected in Part A of P001, including 30/40/60/40/20/20/20/20/20 µg of HPV types 6/11/16/18/31/33/45/52/58 L1VLP with 500 µg aluminium adjuvant per 0.5 mL dose, was used in all 7 phase III clinical studies. GMT, geometric mean titre; SCR, seroconversion rate, SPR, seroprotection rate, n, number of subjects receiving at least one injection

2.2.1. Pharmacokinetics

No clinical pharmacokinetic studies were conducted with the 9vHPV vaccine in support of this Application. Clinical pharmacokinetic studies are not routinely conducted as part of the evaluation of vaccines, as indicated by the CHMP "Guideline on Clinical Evaluation of New Vaccines" (EMEA/CHMP/VWP/164653/2005).

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2.2.3. Pharmacodynamics

Mechanism of action

The pharmacodynamics of a vaccine relate to its interaction with the immune system and is essentially described through immune responses to vaccination. Gardasil 9 is an adjuvanted non-infectious recombinant 9 valent vaccine. It is prepared from the highly purified virus-like particles (VLPs) of the major capsid L1 protein from the same four HPV types (6, 11, 16, 18) in qHPV vaccine Gardasil or Silgard and from 5 additional HPV types (31, 33, 45, 52, 58). It uses the same amorphous aluminium hydroxyphosphate sulphate adjuvant as the qHPV vaccine. The VLPs cannot infect cells, reproduce or cause disease. The efficacy of L1 VLP vaccines is thought to be mediated by the development of a humoral immune response. The assessment of anti-HPV immune responses was restricted to serum antibody responses only, using HPV vaccine type-specific Competitive Luminex Immunoassay (HPV-9 cLIA). The pseudovirion-based neutralization assay was used as supportive and only analysed for study 001. The immunogenicity of the 9vHPV vaccine is described in detail in the Clinical Efficacy section.

Based on epidemiology studies, Gardasil 9 is anticipated to protect against the HPV types that cause approximately: 90% of cervical cancers, more than 95% of adenocarcinoma in situ (AIS), 75-85% of high-grade cervical intraepithelial neoplasia (CIN 2/3), 85-90 % of HPV related vulvar cancers, 90-95 % of HPV related high-grade vulvar intraepithelial neoplasia (VIN 2/3), 80-85% of HPV related vaginal cancers, 75-85 % of HPV related high-grade vaginal intraepithelial neoplasia (VaIN 2/3), 90-95% of HPV related anal cancer, 85-90% of HPV related high-grade anal intraepithelial neoplasia (AIN2/3), and 90% of genital warts.

The indication of Gardasil 9 is based on:

- non-inferior immunogenicity between Gardasil 9 and the qHPV vaccine for HPV Types 6, 11, 16 and 18 in girls and women 9 to 26 years of age; consequently, efficacy for Gardasil 9 against persistent infection and disease related to HPV Types 6, 11, 16, or 18 can be inferred to be comparable to that of the qHPV vaccine;
- demonstration of efficacy against persistent infection and disease related to HPV Types 31, 33, 45, 52 and 58 in girls and women 16 to 26 years of age, and
- demonstration of non-inferior immunogenicity against the Gardasil 9 HPV Types in boys and girls 9- to 15 years of age and men 16- to 26-years of age, compared to girls and women 16-to 26-years of age.

2.2.4. Conclusions on clinical pharmacology

Whereas pharmacokinetics studies are not usually conducted for a vaccine, pharmacodynamics relate to its mechanism of action, which is thought to be mediated by the induction of immune responses against the specific aetiological agent. The VLPs included in the vaccine cannot infect cells, reproduce or cause disease. The assessment of anti-HPV immune responses was restricted to serum antibody responses only, using HPV vaccine type-specific Competitive Luminex Immunoassay (HPV-9 cLIA). The pseudovirion-based neutralization assay was used as supportive and only analysed for study 001. Immunogenicity of Gardasil 9 is described in details in the following section on clinical efficacy.

Clinical efficacy

2.2.5. Dose response study

One formal dose formulation-finding study was conducted as Part A of a pivotal efficacy study (P001) in 16-26 years of age women. In this study, three dose formulations of 9vHPV vaccine were tested, in comparison with qHPV vaccine with respect to 4 original vaccine HPV types. The mid-dose formulation containing 270 µg of total antigens and 500 µg of AAHS adjuvant was selected, based on interim analysis, for all subsequent phase III immunogenicity and efficacy evaluations. This was found acceptable by the CHMP.

See section 2.2.7 for details of the study design.

2.2.6. Main studies

The clinical development program consists of 7 clinical studies. One study (001) was a phase II/III study conducted in two parts A and B, and the others were phase III studies. Four studies are considered pivotal: 001, 002, 003 and 009/GDS01C, and three studies supportive: 005, 006 and 007.

One pivotal efficacy study (Part B of P001) was conducted in 16-26 years of age women to assess efficacy of 9vHPV vaccine against HPV types 31, 33, 45, 52 and 58, using the composite endpoint of CIN2/3, AIS, invasive cervical carcinoma, VIN2/3, VaIN2/3, vulvar cancer or vaginal cancer. Efficacy against HPV 6, 11, 16 and 18 was primarily assessed using a bridging approach that demonstrated non-inferior immunogenicity of the 9vHPV vaccine compared to the qHPV vaccine (Part B of P001, P009/GDS01C).

The pivotal study 002 compared immune responses to the 9vHPV vaccine in women 16-26 years vs. the immune responses of boys and girls 9-15 years of age receiving the same vaccine. The pivotal study 009/GDS01C compared immune responses to Gardasil and the 9vHPV vaccine in subjects 9-15 years old. The pivotal study 003 compared immune responses to 9vHPV vaccine in males 16-26 years old against immune responses in women 16-26 years old.

As mentioned in section 2.2.5, the immunogenicity of the HPV vaccines was measured using 2 methods (see also page 45):

- A competitive Luminex-based immunoassay (cLIA) and
- A pseudovirion-based neutralisation assay (PBNA).

Pivotal Studies

Each study was a multinational and multicentre trial and designed prospectively with concurrent control(s).

The main design features of 7 clinical studies were summarized in the tabular overview and further described as follows (study 003 is described separately after the description of the other pivotal studies):

Study 001

The study was a double-blind, randomized, Gardasil-controlled trial. It assessed immunogenicity, efficacy and safety of 9vHPV vaccine in young women, 16 – 26 years of age. The study was adaptively designed (Part A, Part B) and included 3 substudies:

- Part A: phase IIb Dose-finding substudy evaluated safety and immunogenicity of 3 dose formulations of the 9vHPV vaccine, in comparison with Gardasil (mentioned above).
- Part B: phase III Immunogenicity substudy and Efficacy substudy were conducted following Part A. They compared 9vHPV vs. Gardasil for immunogenicity, efficacy and safety in a 3 dose-regimen. The immunogenicity substudy comprised all subjects enrolled in Part B and represented a subset of the efficacy substudy.

Dose-finding substudy extended from Day 1 through Month 7, and the duration of immunogenicity substudy was 42 months (for efficacy substudy, see 3.4 section).

Study 002

The study included two substudies: Adult-to-adolescent immunobridging substudy compared (pre)adolescents vs. young women with respect to safety and immunogenicity of 9vHPV vaccine, in an open-label non-randomized manner. Lot consistency substudy compared 3 manufacturing lots for immunogenicity of the vaccine in 9-15 year-old girls, in a randomized and double-blinded fashion.

The duration of P002 study was 12 months (for safety).

Study 009/GDS01C

The study compared 9vHPV vs. Gardasil for immunogenicity and safety in 9-15 year-old girls. This was a double-blind randomized trial with the duration of 7 months.

Methods

Study Participants

Study 001 included females 16-26 years of age.

Inclusion criteria included: in good physical health; able to read, understand, and complete the vaccination report card; agrees to provide study personnel with a primary telephone number as well as an alternate telephone number for follow-up purposes; has never had Pap testing or has only had normal Pap test results; has a lifetime history of 1 to 4 male and/or female sexual partners at the time of enrolment OR has 0 male and/or female sexual partner, is 18 years of age or older, and plans to become sexually active within the first 3-6 months of the study; has refrained from douching/vaginal cleansing and using vaginal medications or preparations for 2 calendar days prior to the Day 1 visit and agrees to refrain from these activities for 2 calendar days prior to any future visit that includes collection of study specimens (cervical/genital swabs or Pap test); has refrained from sexual activity (including anal, vaginal, or genital/genital contact whether same sex or opposite sex) for 2 calendar days prior to the Day 1 visit.

Subject agrees to refrain from these sexual activities for 2 calendar days prior to any future visit that includes collection of study specimens (cervical/genital swabs or Pap test); 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 and understands and agrees that during the Day 1 through Month 7 period, she should not have sexual intercourse with males without contraception.

One hundred five centres located in Austria, Brazil, Canada, Chile, Colombia, Denmark, Germany, Hong Kong, Japan, Mexico, New Zealand, Norway, Peru, Republic of Korea, Sweden, Taiwan, Thailand, and the U.S. enrolled subjects into the study.

Study 002 included Boys and Girls Age 9 to 15 Years.

Inclusion criteria: Subject is male or female, between the ages of 9 years and 15 years on the day of enrolment, in good physical health; agrees to provide study personnel with a primary telephone number as well as an alternate telephone number for follow-up purposes; must not yet have had coitarche and does not plan on becoming sexually active during the Day 1 through Month 7 period. Women Age 16 to 26 Years: Same as for study 001.

Seventy-two (72) study centres located throughout Africa, Asia-Pacific, Europe, Latin America, and North America enrolled subjects into the study.

Study 009/GDS01C included 9 to 15 year-old healthy girls, who had not yet coitarche and does not plan on becoming sexually active during the study period, without known allergy to any vaccine component, or history of severe allergic reaction that required medical intervention, or immunosuppressive condition or treatment, or autoimmune condition, did not receive a marketed HPV vaccine, has not participated in an HPV vaccine clinical trial, and has no history of a positive HPV test.

Subjects were recruited to 26 centres in Belgium, Denmark, Finland, Italy, Spain and Sweden.

Treatments

Study 001: Study vaccine was administered as a 0.5-mL intramuscular injection in a three dose regimen (Day 1, Month 2, and Month 6).

Part A: Approximately 1,240 healthy 16- to 26-year-old women were to be randomized in equal numbers to one of the three 9vHPV vaccine dose formulations (low, mid or high dose) or the comparator qHPV vaccine.

Low dose: 20/40/40/20/20/20/20/20/20 µg HPV 6/11/16/18/31/33/45/52/58 VLP with 500 µg aluminum adjuvant/0.5 mL

Mid dose: 30/40/60/40/20/20/20/20/20 µg HPV 6/11/16/18/31/33/45/52/58 VLP with 500 µg aluminum adjuvant/0.5 mL

High dose: 30/40/80/55/30/30/30/30/30 µg HPV 6/11/16/18/31/33/45/52/58 VLP with 500 µg aluminum adjuvant/0.5 mL

Part B: Approximately 13,380 additional healthy 16- to 26-year-old women were to be randomized in equal numbers to the selected 9vHPV vaccine dose formulation chosen from Part A or the comparator qHPV vaccine.

Study 002 and 009/GDS01C: Subjects received one 0.5-mL intramuscular dose of 9vHPV vaccine at Day 1, Month 2, and Month 6. The dose corresponds to the mid-dose in study 001.

The choice of dosing was based on the experience with qHPV.

Objectives

Study 001:

Part A Analysis: Primary Objectives

(1) Objective: To evaluate the tolerability of the 9-valent HPV L1 VLP vaccine when administered to 16- to 26-year-old women.

(2) Objective: To evaluate a formulation of 9-valent HPV L1 VLP vaccine for use in the efficacy evaluation in Part B.

Part B Analysis (Tolerability and Efficacy Analyses Include Part A Subjects Who Received the Selected 9-Valent HPV L1 VLP Vaccine Dose or the Comparator GARDASIL™)

Primary Objectives

(1) Objective: To evaluate the tolerability of the 9-valent HPV L1 VLP vaccine when administered to 16- to 26-year-old women.

(2) Objective: To demonstrate that administration of 9-valent HPV L1 VLP vaccine will reduce the combined incidence of HPV 31-, 33-, 45-, 52-, and 58-related high-grade cervical abnormalities (CIN 2/3), Adenocarcinoma In Situ (AIS), invasive cervical carcinoma, high-grade Vulvar Intraepithelial Neoplasia (VIN 2/3), high-grade Vaginal Intraepithelial Neoplasia (VaIN 2/3), vulvar cancer, or vaginal cancer, compared with Gardasil in 16- to 26-year-old adolescent and young adult women who are seronegative at Day 1 and PCR negative Day 1 through Month 7 to the relevant HPV type.

(3) Objective: To demonstrate that the 9-valent HPV L1 VLP vaccine induces non-inferior GMTs for anti-HPV 6, 11, 16, and 18 compared to Gardasil.

Secondary Objectives

(1) Objective: To demonstrate that administration of 9-valent HPV L1 VLP vaccine will reduce the combined incidence of HPV 31-, 33-, 45-, 52-, and 58-related persistent infection detected in samples from two or more consecutive visits (±1 month visit windows) 6 months or longer apart compared with Gardasil in 16- to 26-year-old adolescent and young adult women who are seronegative at Day 1 and PCR negative Day 1 through Month 7 to the relevant HPV type.

(2) Objective: To demonstrate that 9-valent HPV L1 VLP vaccine is immunogenic with respect to HPV types 31, 33, 45, 52, and 58.

(3) Objective: To demonstrate that the 9-valent HPV L1 VLP vaccine induces non-inferior immune responses with respect to seroconversion percentages for HPV 6, 11, 16, and 18 compared to Gardasil.

(4) Objective: To quantify the amount by which the administration of 9-valent HPV L1 VLP vaccine reduces the combined incidence of HPV 31-, 33-, 45-, 52-, and 58-related cervical, vulvar and vaginal disease compared with Gardasil in 16- to 26-year-old adolescent and young adult women who are seronegative at Day 1 and PCR negative Day 1 through Month 7 to the relevant HPV type(s).

(5) Objective: To evaluate the persistence of anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 immune responses generated by 9-valent HPV L1 VLP vaccine.

(6) Objective: To evaluate the impact of administration of 9-valent HPV L1 VLP vaccine on the incidence of Pap test abnormalities (ASC-US [Positive for High Risk HPV] or worse).

Exploratory efficacy objectives

- to demonstrate the reduction in the combined incidence of HPV-31/33/45/52/58-related persistent infection (PI ⩾12 months duration) in 9vHPV vaccine, relative to qHPV group
- To evaluate whether 9vHPV vaccination reduces the combined incidence of HPV-16/18-related PI (⩾6 months duration) and HPV-16/18-related cervical, vulvar, and vaginal disease
- To evaluate whether a combined incidence of HPV-6/11-related cervical, vulvar, and vaginal disease is comparable in the 9vHPV vs. qHPV vaccine groups
- To evaluate the impact of 9vHPV vaccination on the combined incidence of CIN, AIS, and cervical cancer caused by any HPV type
- To evaluate the impact of 9vHPV vaccination on the combined incidence of vulvar and vaginal disease caused by any HPV type
- To evaluate the efficacy of 9vHPV vaccine against HPV-35/39/51/56/59-related PI (⩾6 months duration) and HPV35/39/51/56/59-related cervical, vulvar, and vaginal disease
- To evaluate the impact of 9vHPV vaccination on the incidence of Pap test abnormalities (ASC-US [Positive for High Risk HPV] or worse) related to HPV Types 31, 33, 45, 52, and 58
- To evaluate the impact of 9vHPV vaccination on the incidence of cervical biopsy and cervical definitive therapy treatments

Study 002:

Primary Safety Objective: To evaluate the tolerability of the 9-valent HPV L1 VLP vaccine in preadolescent and adolescent boys and girls 9 to 15 years of age and young women 16 to 26 years of age.

Primary Immunogenicity Objectives:

Adolescent-Adult Immunobridging Substudy

(1) To demonstrate that administration of the 9-valent HPV L1 VLP vaccine induces non-inferior GMTs for serum anti-HPV 6, anti-HPV 11, anti-HPV 16, anti-HPV 18, anti-HPV 31, anti-HPV 33, anti-HPV 45, anti-HPV 52, and anti-HPV 58 in preadolescent and adolescent girls 9 to 15 years of age compared to young women 16 to 26 years of age.

(2) To demonstrate that administration of the 9-valent HPV L1 VLP vaccine induces non-inferior GMTs for serum anti-HPV 6, anti-HPV 11, anti-HPV 16, anti-HPV 18, anti-HPV 31, anti-HPV 33, anti-HPV 45, anti-HPV 52, and anti-HPV 58 in preadolescent and adolescent boys 9 to 15 years of age compared to young women 16 to 26 years of age.

Manufacturing Lot Consistency Substudy

(1) To demonstrate that the Final Manufacturing Process (FMP) results in 9-valent HPV L1 VLP vaccine that induces consistent serum anti-HPV 6, anti-HPV 11, anti-HPV 16, anti-HPV 18, anti-HPV 31, anti-HPV 33, anti-HPV 45, anti-HPV 52, and anti-HPV 58 responses.

Secondary Objectives:

Adolescent-Adult Immunobridging Substudy

(1) To demonstrate that the 9-valent HPV L1 VLP vaccine induces non-inferior immune responses with respect to seroconversion percentages to HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 in preadolescent and adolescent girls 9 to 15 years of age compared to young women 16 to 26 years of age.

(2) To demonstrate that the 9-valent HPV L1 VLP vaccine induces non-inferior immune responses with respect to seroconversion percentages to HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 in preadolescent and adolescent boys 9 to 15 years of age compared to young women 16 to 26 years of age.

Manufacturing Lot Consistency Substudy

(1) To demonstrate that the FMP results in 9-valent HPV L1 VLP vaccine that induces consistent seroconversion percentages to HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58.

Study 009/GDS01C

Primary Objective

To demonstrate that administration of the 9vHPV vaccine induces non-inferior Geometric Mean Titres (GMTs) for serum anti-HPV 16 and anti-HPV 18 compared to qHPV vaccine in preadolescent and adolescent girls 9 to 15 years of age.

Secondary Objectives

To evaluate the tolerability of the 9vHPV vaccine in preadolescent and adolescent girls 9 to 15 years of age.

To summarise humoral immune responses (including anti-HPV 6, 11, 16, 18, GMTs and seroconversion rates at 4 weeks post-dose 3) in preadolescent and adolescent girls 9 to 15 years of age who received 9vHPV vaccine or qHPV vaccine.

Exploratory Objective

To summarise humoral immune responses (including anti-HPV 31, 33, 45, 52, 58 GMTs and seroconversion rates at 4 weeks post-dose 3) in preadolescent and adolescent girls 9 to 15 years of age who received 9vHPV vaccine.

The objectives of the pivotal studies are in agreement with the scientific advice, and the methodology used is in agreement with the development of Gardasil.

Outcomes/endpoints

Study 001

Efficacy: The protocol specified that the primary analysis of efficacy was to be conducted in the per-protocol efficacy (PPE) population. This cohort consisted of subjects who received all 3 vaccinations, did not deviate from the study protocol in ways that could potentially interfere with the efficacy of the vaccine, and were seronegative at baseline and PCR negative at baseline and during the 6-month vaccination regimen and for 1 month thereafter (to allow for induction of immune responses to Dose 3 of the vaccine) to the relevant HPV type(s). Cases of the primary endpoint were counted starting after Month 7. The following specimens were collected from study participants for the purpose of detecting vaccine-type HPV deoxyribonucleic acid (DNA) or clinical disease: (1) cervico-vaginal and external genital swabs; (2) ThinPrep™Pap test; (3) cervical or external genital biopsy if clinically indicated; (4) endocervical curettage specimen at the investigator's discretion; and (5) definitive therapy specimen if clinically indicated. A blinded Pathology Panel evaluated all biopsies according to a standard operating procedure until consensus diagnoses were obtained. Primary efficacy cases of CIN 2/3 or worse, VIN2/3 or worse, and VaIN 2/3 or worse were defined if, on a single biopsy tissue block, both of the following

conditions were met: (1) HPV 31 DNA, HPV 33 DNA, HPV 45 DNA, HPV 52 DNA and/or HPV 58 DNA was detected in biopsy thin sections using Merck's Biopsy Thin-Section PCR Assay; and (2) the consensus diagnosis of the Program's Pathology Panel was CIN 2, CIN 3, AIS, cervical cancer, VIN2/3, VaIN 2/3, vulvar cancer, or vaginal cancer.

The clinical efficacy endpoints are in agreement with those used in the clinical development of Gardasil, and have been further discussed in scientific advice.

Immunogenicity: Serum anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 titres were measured using a HPV-9 competitive Luminex Immunoassay (HPV-9 cLIA). The following endpoints were collected from each study subject to assess immunogenicity: 1) cLIA titres for each of the vaccine HPV types; 2) seroconversion status (i.e., above or below serostatus cut off) for each of the vaccine HPV types. All subjects that were part of the defined per protocol immunogenicity (PPI) population were included in the immunogenicity summary. Serum samples were collected from all subjects at Day 1 and Month 7. Additional samples were collected at Month 12, Month 24, Month 36, and Month 42 to assess persistence of antibody responses. The primary time point for immunogenicity analysis was at Month 7.

The serostatus cut-off is the antibody titre level within the assay's quantifiable range that reliably distinguishes "negative" from "positive" samples. The HPV-9 cLIA serostatus cut-offs for HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58 are 30, 16, 20, 24, 10, 8, 8, 8 and 8 mMU/mL, respectively.

Two versions of the HPV-9 competitive Luminex immunoassay (HPV-9 cLIA) were used in the 001 study: Version 1.0 representing the pre-validated assay, and Version 2.0 representing the fully validated assay used to assess immunogenicity for Phase III. One difference between Version 2.0 and Version 1.0 is the different dilution rule. Version 1.0 of the HPV-9 cLIA was used for Part A interim immunogenicity analysis of baseline and PD2 specimens to support dose selection. Subsequently, Version 2.0 of the HPV-9 cLIA assay was applied to Part B of the study to support the primary, secondary, and exploratory immunogenicity objectives of the study. In the per-protocol efficacy analysis, baseline HPV serostatus, as determined by testing using the HPV-9 cLIA assay, will be used to include/exclude eligible subjects. While material discrepancy in HPV baseline seropositivity as determined by the two versions of the HPV-9 cLIA is not expected, baseline samples for Part A subjects who received either the selected V503 dose formulation or qHPV vaccine were re-tested using Version 2.0 of the HPV-9 cLIA. Thus, the HPV-9 cLIA Version 2.0 is consistently used to determine baseline serostatus for both Part A and Part B subjects in order to allow data from Part A and Part B subjects to be combined for the efficacy analyses.

In addition, a subset of subjects in the immunogenicity subset were analysed using the pseudovirion-based neutralisation assay (PBNA).

Safety: The following measures were collected from each study subject to assess safety: 1) temperatures (within 5 days following any vaccination); 2) all adverse events (within 14 days following any vaccination); 3) all serious adverse experiences that occurred from Day 1 through 180 days following the last vaccination; 4) all serious adverse experiences that resulted in death or were determined to be related to the study vaccine or study procedure that occurred at any time during the study. All subjects that received at least one injection of study vaccine and had safety follow-up data were included in the safety summary. In addition to the above safety endpoints, this CSR summarizes: (1) new medical conditions; (2) serious adverse experiences observed during pregnancy and lactation; (3) pregnancy outcomes; and (4) serious adverse experiences in infants (of study subjects) potentially exposed to test product.

Study 002

Immunogenicity: The same immunogenicity endpoints were used as in study 001, except that the no additional serum samples were taken after month 7.

Safety: The following measures were collected from each study subject to assess safety: 1) temperatures (within 5 days following any vaccination); 2) all adverse events (within 14 days following any vaccination); 3) all serious adverse experiences (SAEs) that occurred from Days 1 through 180 following the last vaccination; 4) all SAEs that resulted in death or were determined to be related to the study vaccine that occurred at any time during the study. All subjects who received at least one injection of study vaccine and had safety follow-up data were included in the safety summary.

Study 009/GDS01C

Immunogenicity: The same immunogenicity endpoints were used as in study 001, except that the no additional serum samples were taken after month 7.

Safety: The same safety endpoints as in study 002 were used in study 009/GDS01C.

Across studies, the serological methods are the same as for Gardasil development, and are considered relevant and well established.

Sample size

Study 001

The study sample size was determined to provide sufficient statistical power to demonstrate success against the primary efficacy hypothesis if the 9vHPV vaccine is truly efficacious.

A total sample size of 14,000 subjects (Part A = 620; Part B = 13,380) randomized to either the 9v HPV vaccine or the qHPV vaccine on a 1:1 allocation ratio provides the study a >90% power to demonstrate success on the primary efficacy hypothesis based on a test with one-sided α=0.025 level of significance. The power and sample size were determined based on the following assumptions:

– Efficacy of the 9vHPV vaccine relative to placebo is 88%;

– Efficacy of the 9vHPV vaccine relative to the qHPV vaccine against HPV types 31, 33, 45, 52, and 58 is 83% under the assumption that the qHPV vaccine has cross-protection efficacy of 30% relative to placebo against these HPV types.

With these assumptions, 30 cases of the primary efficacy endpoint need to be accrued to have >90% power to succeed on the test of the primary efficacy hypothesis at α=0.025 level of significance based on a fixed-event design. A total sample size of 14,000 subjects will provide at least 30 cases of the primary efficacy endpoint based on the following assumptions:

– $\leqslant$23% exclusion rate from the PPE population due to Day 1 seropositivity and/or Day 1 through Month 7 PCR-positivity to HPV types 31, 33, 45, 52, and 58;

– $\leqslant$10% attrition rate between Day 1 through Month 7;

– $\leqslant$5% attrition rate post Month 7;

– 0.35 per 100 person-years incidence of the primary efficacy endpoint in the qHPV vaccine group; and

– Accrual of at least 30 months post randomization follow-up time on at least 50% of subjects randomized.

Study 002

Immunobridging hypotheses will be tested by comparing the approximately 600 preadolescent and adolescent girls (or boys) vs. the approximately 400 young women (16 to 26 years of age) who received the same lot of vaccine. The sample size for the preadolescent and adolescent group (~600 per group) is primarily driven by the lot consistency objective and also by consideration of the overall safety data base in 9- to 15-year-old subjects. One-sided 2.5% significance level is used for the calculations. The power and sample size are based on the following assumptions: 1) the exclusion rates for PPI population are approximately 20% for the 9- to 15-year-old girls and boys group and 40% for the 16- to 26-year-old young women group, 2) a standard deviation (SD) of the natural-log-transformed titres of 1.2, and 3) non-inferiority margin for GMT ratio is 1.5 fold. The estimates of exclusion rates and SD are based on data from previous qHPV vaccine studies.

A sample size of 400 young women and 600 preadolescent and adolescent girls has 91% power to show non-inferior Month 7 GMTs for preadolescent and adolescent girls vs. 16- to 26-year-old young women if the underlying GMT ratio is 1.0 for the 4 original types (HPV 6, 11, 16, and 18) and also 1.0 for the 5 new types (HPV 31, 33, 42, 52, and 58). Since higher anti-HPV 6, 11, 16 and 18 GMTs have been observed with qHPV vaccine in preadolescent and adolescent girls and boys than in 16-to 26-year-old young women (GMT ratios ranged from 1.7 to 2.7 across the 4 HPV types), it is possible that in this study, the GMT ratios for these 4 original types and also the 5 new types (by the same mechanism) will be higher than 1.0. The power will increase to 95% if the underlying GMT ratio is 1.2 for the 4 original types and 1.0 for the 5 new types. The power may reach >99% if the underlying GMT ratio is 1.2 for both the original and new types.

Non-inferior Month 7 GMTs for 9- to 15-year-old boys vs. 16- to 26-year-old young women will be tested only if the GMT comparisons between 9- to 15-year-old girls and 16- to 26-year-old young women reach statistical significance. The statistical power for meeting the primary immunogenicity hypothesis in all 9 HPV types for 9- to 15-year-old boys vs. 16- to 26-year-old young women would be at least, (91%)2=83% assuming true GMT ratios 1.0 for all 9 types, (95%) 2=90% assuming true GMT ratios 1.2 for original types (6, 11, 16 and 18) and 1.0 for new types (31, 33, 42, 52, and 58), and >99% assuming true GMT ratios 1.2 for all 9 types.

Study 009/GDS01C

This study was intended to randomize equally 600 girls (9 to 15 years of age) into each of the 2 groups (9vHPV vaccine vs. qHPV vaccine). The primary set of subjects for the analysis of the immune responses was the Per Protocol Set. It was expected that there would be an approximately 20% exclusion rate from the PPS. Thus, the primary analysis would include 480 girls (240 in each group). The non-inferiority margin is 0.67, the true GMT ratio was assumed to be 1 and the standard deviation was estimated at 1.2 for both the HPV 16 and 18 post-vaccination titres (natural log scale). Based on 240 evaluable subjects per group and the above elements, the study has over 90% power to demonstrate the non-inferiority of the 9vHPV vaccine compared to qHPV vaccine for HPV 16 and 18.

The estimations of exclusion rate and the standard deviation were based on data from previous qHPV vaccine studies. The power of the study was calculated using PASS 2008 software based on the assumption of log-normality of the post-vaccination titres.

All sample size calculations were based on reasonable assumptions.

Randomisation

Study 001

In Part A or Part B, subjects received an allocation number from an allocation schedule generated by the Clinical Biostatistics department of the Sponsor. There were separate allocation schedules for Part A and Part B. The randomization was balanced within sites. An Interactive Voice Response System (IVRS) was used to allocate

study subjects and assist with the vaccine supply management at the study site. At the first visit, study personnel accessed the IVRS after the subject had signed informed consent (or for minors after a subject's parent/legal guardian had signed informed consent and the subject had signed assent), and after the subject had met all inclusion and none of the exclusion criteria. The IVRS assigned the subject an allocation number (AN) and a unique vial identification number for the vial of clinical material that the subject was to receive at that visit. The IVRS assigned the appropriate clinical material based on the subject's vaccination group. The study personnel accessed IVRS at each subsequent vaccination visit for assignment of a unique vial identification number of the clinical material from the appropriate vaccination group to be administered to the subject. ANs were subject-specific and were not reused for any reason. ANs for subjects who discontinued or withdrew from the study were not reassigned.

Study 002

Enrolment was stratified by age and gender. Among the 9- to 15-year-old subjects, enrolment was stratified approximately 2:1 for 9- to 12-year-olds and 13- to 15-year-olds. This was to ensure that the tolerability profile of the vaccine among the younger subjects is clearly defined.

Specifically, 3 allocation schedules were generated by the Sponsor – one for each of the following cohorts:

- 9- to 15-year-old females (~1800 subjects): the allocation schedule was stratified 2:1 for 9- to 12-year-olds and 13- to 15-year-olds; these subjects were randomized within each age stratum in a 1:1:1 ratio to receive 1 of 3 FMP vaccine lots (Lot 1, Lot 2, or Lot 3) using centralized randomization; subjects, site personnel and Sponsor were blinded to vaccine lot allocation
- 9- to 15-year-old males (~600 subjects): the allocation schedule was stratified 2:1 for 9- to 12-year-olds and 13- to 15-year-olds; these subjects all received vaccine Lot 1
- 16- to 26-year-old females (~400 subjects): no age strata were included in the allocation schedule; these subjects all received vaccine Lot 1

As in study 001, an Interactive Voice Response System (IVRS) was used to allocate study subjects, and assign each subject an AN.

Study 009/GDS01C

A central randomization system (implemented through an Interactive Web Response System [IWRS]) assigned the subject a vaccine group (blinded) and an allocation number according to the randomized allocation schedules and then subsequently assigned a unique vaccine kit number corresponding to the vaccine group. The randomized allocation schedule was stratified in 2 age strata (9 to 12 years of age, and 13 to 15 years of age, at the time of enrolment) with a capping at 300 subjects per stratum and was based on balanced randomization blocks of size 6 (i.e. 50 blocks of size 6 per stratum). Subjects were randomized in a 1:1 ratio within each age stratum to 9vHPV vaccine or qHPV vaccine. A single subject could not be assigned more than 1 allocation number. In addition, at each subsequent administration of study vaccine, the study personnel requested through the IWRS the assignment of a vaccine kit number corresponding to the subject's vaccine group.

Blinding (masking)

Study 001

This was a double-blind study with in-house blinding procedures. Subjects, investigators, laboratory staff and the Sponsor were blinded to vaccine allocation. The clinical materials GARDASIL™ and the 3 doses of 9-valent HPV L1 VLP vaccine were visually indistinguishable, and were supplied in identical vials. Clinical, statistical and

data management study personnel at the Sponsor, involved in study conduct, remained blinded to subject vaccination group allocations for Part A and Part B subjects until primary efficacy analysis. The exception was unblinded personnel who provided data summaries for dose selection and DSMB meetings but was otherwise not associated with the conduct of the study or the design of any of the statistical analyses for the study (other than those requested by the DSMB).

In Part A, sites were to contact IVRS at the completion of each subject's Month 7 visit to determine those subjects from Part A who were to continue in the study to at least Month 42 and those who were to complete the study at their Month 7 visit. No vaccination group information for the continuing subjects was released to the study sites, and subjects continuing beyond Month 7 remained randomised between the two continuing vaccination groups. The formal statistical test of the Part A hypothesis based upon Month 7 data was conducted at the time the database was unblinded for the primary efficacy analysis.

In addition, the Pathology Panel was blinded to the vaccination group assignment of study subjects, and to results of HPV typing analysis of specimens of study subjects, throughout the duration of the study.

Study 002

Given that the study included comparisons of 9vHPV vaccine across distinctly different age and gender groups, a full double-blind design was not possible. Within the Immunobridging Substudy boys 9-15 years and, young women 16-26 years old was assigned open-label treatment with the 9vHPV vaccine (of the same FMP lot). Within the Manufacturing Lot Consistency Substudy however, girls 9-15 years were randomised to 1 of 3 different FMP lots of the 9vHPV vaccine with subjects, investigators (and staff), laboratory staff, and Sponsor blinded to FMP lot number throughout the study until the unblinding of the database.

In addition the laboratory staff was to remain blinded to age and gender of all subjects for the duration of the study.

Study 009/GDS01C

The study was performed in a double-blind fashion. Subjects, investigators, and the Sponsor, with limited exceptions (e.g. Pharmacovigilance and Risk Management Department) were blinded to vaccine allocation. The two study vaccines were visually identical and were presented in an indistinguishable packaging. Laboratory personnel conducting HPV assays were blinded to all subjects' age, as well as the vaccination group.

Overall, Study 001 and Study 009/GDS01C were both performed in a double-blind fashion. Blinding procedures were appropriate and in Study 001 the blinding was maintained for those subjects randomised to the selected dose and comparator who continued in the study beyond Month 7. The mix of open-label and double blind treatment in Study 002 is acceptable.

Statistical methods

Study 001

The study used a seamless Phase II/III adaptive design. Based on an interim analysis of immunogenicity data in the phase II dose selection part (Part A), one dose was selected for evaluation in the phase III part (Part B). The evaluation of primary safety and efficacy objectives for the 9v HPV vaccine was based on combined data from subjects enrolled in Part A who received the selected 9v HPV vaccine dose or the comparator and subjects enrolled in Part B. The primary immunogenicity analyses for Part B was the formal comparison of the selected 9-valent HPV L1 VLP vaccine to the qHPV control and included those subjects enrolled in Part B only.

Part B had a fixed event design whereby the primary efficacy analysis was to be conducted after at least 30 cases of the primary efficacy endpoint (HPV 31/33/45/52/58-related high-grade cervical abnormalities (CIN 2/3), Adenocarcinoma In Situ (AIS), invasive cervical carcinoma, high-grade Vulvar Intraepithelial Neoplasia (VIN 2/3), high-grade Vaginal Intraepithelial Neoplasia (VaIN 2/3), vulvar cancer, or vaginal cancer) had been observed.

Vaccine efficacy (VE), defined as 100%*(1-relative risk) and equivalent to the percent reduction in the risk of becoming a case of a particular endpoint in the group vaccinated with 9-valent HPV L1 VLP vaccine relative to the risk in the qHPV group, was computed using exact methods. The statistical criterion for success with respect to the primary efficacy hypothesis required that the lower bound of the confidence interval for vaccine efficacy exclude 25% for the primary efficacy endpoint. The primary efficacy hypothesis was tested at the á=0.025 (1-sided) level.

For every composite efficacy endpoint, an estimate of vaccine efficacy with 95% confidence intervals was also provided for each HPV type and/or by lesion type. In addition to computing point and CI estimates of VE, Kaplan-Meier time-to-event plots were estimated for selected efficacy endpoints.

The primary immunogenicity endpoints were geometric mean titres (GMTs) corresponding to HPV types 6, 11, 16, and 18 at Week 4 Postdose 3 (Month 7). The hypotheses of non-inferiority of GMTs for HPV types 6, 11, 16 and 18 were based on one-sided tests of non-inferiority comparing GMTs for each component. Four ANOVA models (one per HPV type) with a response of log individual titres and a fixed effect for vaccination group was used. Each hypothesis was tested at the á=0.025 level (1-sided).

In the primary analyses a per-protocol approach was used. Per Protocol Efficacy (PPE) Populations consisted of subjects who received all 3 doses of the 9vHPV vaccine or the qHPV vaccine within 1 year; had Month 7 PCR results on swab samples collected within 14 to 72 days post-dose 3; were HPV-naïve (i.e., seronegative at Day 1 and PCR negative from Day 1 through Month 7) to the vaccine HPV type being analysed (HPV-naïve to both types 6 and 11 in analysis of HPV 6-related and HPV 11-related endpoints); and did not violate the protocol in ways that could interfere with the evaluation of immune response to injections of the 9vHPV or qHPV vaccines.

In the PPE population endpoint cases were counted starting after Month 7.

To support the results of the analyses based on the PPE population, analyses were performed on the HPV-naïve type-specific (HN-TS), the full analysis set (FAS) and the All HPV Naïve Population (All-HN). The HN-TS population consisted of subjects who received at least 1 dose of the 9vHPV or qHPV vaccines, had at least 1 follow-up visit after Day 1 and were HPV-naïve at Day 1 to the HPV type being analysed. To be included in the FAS, subjects should have received at least 1 dose of the 9vHPV or qHPV vaccines and had at least 1 follow-up visit after Day 1. The All-HN population included only subjects who were seronegative and PCR-negative at enrolment to all 9 vaccine HPV types; were PCR-negative at enrolment to all other non-vaccine HPV types for which PCR assays were available; and had a normal Pap test result at enrolment.

Per Protocol Immunogenicity (PPI) populations consisted of subjects who were PPE-population-eligible and had their vaccination visits within acceptable day ranges relative to Day 1 and had at least one Month 7 serology result within 21 to 49 days post-dose 3. To support primary analyses they were repeated based on the All (HPV Type-specific) Naïve Subjects with Serology (ANSS) population. ANSS consisted of subjects who received all 3 doses of 9vHPV or qHPV vaccine; had Month 7 PCR results within 14 to 72 days post-dose 3; were HPV-naïve to the vaccine HPV type being analysed (HPV-naïve to both types 6 and 11 in analysis of HPV 6-related and HPV 11-related endpoints); and had an evaluable post-dose 3 serology result.

To support Part B immunogenicity secondary objectives analyses were also based on the following analysis populations; the Day 1 Seronegative and PCR Positive (S0P1), Day 1 Seropositive and PCR Negative (S1P0) and, Day 1 Seropositive and PCR Positive (S1P1).

All safety analyses were performed on the All-Subjects-as-Treated (ASaT) population that included all randomized subjects who had received at least 1 injection of the 9vHPV or qHPV vaccine and had follow-up data.

No multiplicity adjustments were implemented. Declaration of study success required demonstration of success on both the primary efficacy hypothesis and the primary Part B immunogenicity hypothesis. No efficacy data were summarized during the Part A interim analysis. The primary immunogenicity analysis in Part B was conducted independently from the analysis in Part A. Regarding the multiple hypotheses for HPV types 6, 11, 16 and 18 this was addressed by requiring success for all 4 HPV types (thereby controlling the overall alpha level).

A number of additional analyses that were not specified in the Statistical Analysis Plan were conducted in order to present additional and broader perspective on: 1) prophylactic efficacy expected to be conferred by the 9vHPV vaccine; and 2) therapeutic efficacy that is not expected to be conferred by the 9vHPV vaccine.

No interim analyses were planned nor performed for Part B.

The primary analyses are based on data through the visit cut-off date (of 10-Apr-2013). The study database was locked at 26-Jul-2013.

Study 002

The primary and secondary immunogenicity analyses were performed in type-specific per-protocol immunogenicity populations. Each vaccine component (i.e. HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58) was analysed separately. The analysis of the Day 1 through Month 7 serum was conducted after the database for the Base Period (including analysis of Day 1 and Month 7 serum and safety follow-up through Month 12) was locked and unblinded for lot information.

To be included in the primary immunogenicity analysis for the HPV 6 and HPV 11 components, subjects must be seronegative to both HPV 6 and 11 at Day 1 and (for 16- to 26-year-old women) must be PCR negative to HPV 6 and 11 from Day 1 through Month 7. To be included in the primary immunogenicity analysis for the other vaccine HPV types, subjects were required to be seronegative at Day 1 and (for 16- to 26-year-old women) PCR negative from Day 1 through Month 7 only for the HPV type being analysed. In addition, subjects must have received all 3 doses and have at least 1 post-dose 3 serology result. Subjects with any protocol violation that could interfere with the evaluation of immune response was excluded from the primary immunogenicity analysis.

The immunobridging and manufacturing lot consistency sub-studies were considered separately.

Within the Immunobridging Sub study the primary non-inferiority hypothesis with respect to anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 GMTs at 4 weeks post dose 3 in 9- to 15-year-old boys or girls compared to 16- to 26-year old young women was tested by constructing a 95% confidence interval for the ratio of GMTs. The statistical criterion for non-inferiority required that the lower bound of two-sided 95% CI of GMT ratio (boys/young women or girls/young women) be greater than 0.67 for each HPV type.

The primary hypotheses of non-inferiority of GMTs for each of HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 was addressed by 9 one-sided tests of non-inferiority (one corresponding to each HPV type) conducted at the α=0.025 level (1-sided). The test was performed using an analysis of variance (ANOVA) model with a response of log individual titres and a fixed effect for comparison group.

For immunobridging primary hypotheses, success was required on all 9 vaccine HPV types. For the co-primary hypotheses of non-inferiority of GMTs a closed stepwise testing procedure was used with the non-inferiority hypothesis of GMTs in girls vs. young women tested first and in boys vs. young women tested second, to control the overall Type I error rate at 0.025 (1-sided).

The secondary non-inferiority hypothesis with respect to seroconversion to HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 by 4 weeks post dose 3 in 9- to 15-year-old boys or girls compared to 16- to 26-year old young women was tested by constructing a 95% confidence interval for the difference in seroconversion percentages.

Within the Manufacturing Lot Consistency Sub study the primary hypothesis regarding consistency of the 3 Final manufacturing process (FMP) lots of 9vHPV vaccine with respect to the GMTs to HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 at 4 weeks post-dose 3, was addressed by 3 pair-wise comparisons (Lot 1 vs. Lot 2, Lot 1 vs. Lot 3, and Lot 2 vs. Lot 3) for each HPV type (27 comparisons total). Each pair-wise comparison tested the equivalence of the 2 lots (within 2-fold) using 2 one-sided tests at the 0.025 level. An ANCOVA model was used with a response of log individual titres and fixed effects for vaccine lot and age strata. Lot consistency was to be concluded if the two-sided 95% CI of the ratio of GMTs for each of the three pairs of lots was contained within the interval (0.5, 2.0).

The secondary hypothesis regarding consistency of the 3 FMP lots of 9vHPV vaccine with respect to the percentage of subjects who seroconvert for each HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 by 4 weeks post dose 3 was addressed by 3 pair-wise comparisons for each vaccine HPV type (27 comparisons total). Each pair-wise comparison tested the equivalence of the 2 lots (within an equivalence margin of 5 percentage points) using 2 one-sided tests at the 0.025 level. These comparisons were tested using the method of Miettinen and Nurminen, stratified by age strata.

All subjects who received at least 1 study vaccination and had follow-up data were included in the primary safety analysis.

There was no change in the analyses planned for this study. Protocol V503-002 has been extended through Month 36 to assess HPV antibody persistence in preadolescent and adolescent girls and boys. The analysis of the Month 12 through Month 36 serum was to take place at the end of the V503-002-10 Study Extension. The study extension 002-10 is complete.

Study 009/GDS01C

The primary hypotheses of non-inferiority of GMTs for HPV types 16 and 18 were addressed by 2 one-sided tests of non-inferiority (one corresponding to each HPV type) conducted at α=0.025 level (1-sided). Each test was conducted using an ANOVA model with a response of log individual titres and a fixed effect for group and age strata (as per randomization). No multiplicity adjustments were implemented based on that study success required that non-inferiority had been shown for both HPV types 16 and 18.

The immunogenicity analyses of the primary and secondary endpoints were performed on the Per Protocol Set (PPS) in initially seronegative subjects (primary analysis) and on the All Type-Specific Naïve Subjects with Serology (ANSS) Set in initially seronegative subjects (supportive analysis).

To be included in the PPS subjects were required to have received all 3 vaccinations, have provided Month 7 serology result within 21 to 49 days post dose 3, be seronegative to the appropriate HPV type at Day 1 and, have no other protocol violations that could interfere with the evaluation of subject's immune response to the study vaccine. To be included in the PPS for HPV 6 and 11, subjects had to be seronegative to both HPV 6 and 11 at Day 1.

To be included in ANSS subjects were required to have received all 3 vaccinations, have provided post dose 3 serology data and be seronegative to the appropriate HPV type at Day 1. To be included in the ANSS set for HPV 6 and 11, subjects had to be seronegative to both HPV 6 and 11 at Day 1.

Secondary endpoints were evaluated by descriptive analysis in each group with within group two-sided 95% CIs for rates based on the exact method for binary variables (according to D. Collett) and with CI for GMT based on Students *t* distribution after log transformation of individual titres. The method of Miettinen and Nurminen stratified by age strata was used to determine the 95%CI of differences in seroconversion rates.

Analyses of safety were based on all subjects who received at least 1 study vaccination and had safety follow-up data.

No interim analysis was planned nor performed.

There were no protocol amendments implemented during the course of the study. No changes in the conduct of the study and in the planned analyses were decided. As more than 98% of the subjects were white, the planned analysis of the immunogenicity endpoints by race was not performed.

Results

Participant flow

Study 001

The study participant distribution is summarised in the following tables:

Table 2. Disposition of Subjects (Day 1 to Month 7) (All Randomized Subjects, Dose-Ranging Substudy)

	Low-Dose 9vHPV Vaccine		Mid-Dose 9vHPV Vaccine		High-Dose 9vHPV Vaccine		qHPV Vaccine		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	315		307		310		310		1,242	
Vaccinated at										
Vaccination 1	312	(99.0)	307	(100.0)	310	(100.0)	310	(100.0)	1,239	(99.8)
Vaccination 2	305	(96.8)	300	(97.7)	306	(98.7)	305	(98.4)	1,216	(97.9)
Vaccination 3	300	(95.2)	291	(94.8)	297	(95.8)	300	(96.8)	1,188	(95.7)
Trial Disposition										
Completed	295	(93.7)	290	(94.5)	296	(95.5)	297	(95.8)	1,178	(94.8)
Discontinued	20	(6.3)	17	(5.5)	14	(4.5)	13	(4.2)	64	(5.2)
Adverse Event	1	(0.3)	1	(0.3)	0	(0.0)	0	(0.0)	2	(0.2)
Lost To Follow-Up	12	(3.8)	8	(2.6)	9	(2.9)	7	(2.3)	36	(2.9)
Protocol Violation	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.1)
Withdrawal By Subject	7	(2.2)	8	(2.6)	5	(1.6)	5	(1.6)	25	(2.0)
Subject Study Medication Disposition										
Completed	300	(95.2)	291	(94.8)	297	(95.8)	300	(96.8)	1,188	(95.7)
Did Not Take Study Medication	3	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.2)
Discontinued	12	(3.8)	16	(5.2)	13	(4.2)	10	(3.2)	51	(4.1)
Adverse Event	2	(0.6)	1	(0.3)	0	(0.0)	0	(0.0)	3	(0.2)
Lost To Follow-Up	6	(1.9)	8	(2.6)	9	(2.9)	5	(1.6)	28	(2.3)
Pregnancy	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.1)
Protocol Violation	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.1)
Withdrawal By Subject	4	(1.3)	7	(2.3)	4	(1.3)	3	(1.0)	18	(1.4)
Protocol Milestone										
Continuing Into Next Trial Segment	2	(0.6)	287	(93.5)	0	(0.0)	297	(95.8)	586	(47.2)
Not Continuing Into Next Trial Segment	293	(93.0)	4	(1.3)	296	(95.5)	1	(0.3)	594	(47.8)
Unknown	20	(6.3)	16	(5.2)	14	(4.5)	12	(3.9)	62	(5.0)

Each subject is counted once for Trial Disposition, Study Medication Disposition, Protocol Milestone based on the latest corresponding disposition record.

Unknown: A disposition record did not exist at the time of reporting.

Two subjects from the low-dose group were report as continuing into the next segment of the study and they did not receive further vaccinations.

Table 3. Disposition of Subjects (Day 1 to Month 7) (All Randomized Subjects, Efficacy Substudy)

	9vHPV Vaccine		qHPV Vaccine		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	7,106		7,109		14,215	
Vaccinated at						
Vaccination 1	7,099	(99.9)	7,105	(99.9)	14,204	(99.9)
Vaccination 2	7,015	(98.7)	7,015	(98.7)	14,030	(98.7)
Vaccination 3	6,928	(97.5)	6,934	(97.5)	13,862	(97.5)
Trial Disposition						
Completed	6,862	(96.6)	6,854	(96.4)	13,716	(96.5)
Discontinued	244	(3.4)	255	(3.6)	499	(3.5)
Adverse Event	6	(0.1)	2	(0.0)	8	(0.1)
Lost To Follow-Up	126	(1.8)	128	(1.8)	254	(1.8)
Physician Decision	3	(0.0)	2	(0.0)	5	(0.0)
Protocol Violation	4	(0.1)	4	(0.1)	8	(0.1)
Withdrawal By Subject	105	(1.5)	119	(1.7)	224	(1.6)
Subject Study Medication Disposition						
Completed	6,928	(97.5)	6,934	(97.5)	13,862	(97.5)
Did Not Take Study Medication	7	(0.1)	4	(0.1)	11	(0.1)
Discontinued	171	(2.4)	171	(2.4)	342	(2.4)
Adverse Event	8	(0.1)	4	(0.1)	12	(0.1)
Lost To Follow-Up	92	(1.3)	81	(1.1)	173	(1.2)
Physician Decision	2	(0.0)	4	(0.1)	6	(0.0)
Pregnancy	2	(0.0)	1	(0.0)	3	(0.0)
Protocol Violation	1	(0.0)	4	(0.1)	5	(0.0)
Withdrawal By Subject	66	(0.9)	77	(1.1)	143	(1.0)
Protocol Milestone						
Continuing Into Next Trial Segment	6,857	(96.5)	6,852	(96.4)	13,709	(96.4)
Not Continuing Into Next Trial Segment	10	(0.1)	8	(0.1)	18	(0.1)
Unknown	239	(3.4)	249	(3.5)	488	(3.4)

Each subject is counted once for Trial Disposition, Study Medication Disposition, Protocol Milestone based on the latest corresponding disposition record.

Unknown: A disposition record did not exist at the time of reporting.

There are no major differences between the groups, and no striking discontinuations.

Table 4. Disposition of Subjects (> Month 7 to Month 42) (All Randomized Subjects, Efficacy Substudy)

	9vHPV Vaccine		qHPV Vaccine		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	6,102		6,124		12,226	
Trial Disposition						
Completed	5,502	(90.2)	5,542	(90.5)	11,044	(90.3)
Discontinued	600	(9.8)	582	(9.5)	1,182	(9.7)
Adverse Event	4	(0.1)	3	(0.0)	7	(0.1)
Lost To Follow-Up	328	(5.4)	301	(4.9)	629	(5.1)
Physician Decision	1	(0.0)	3	(0.0)	4	(0.0)
Protocol Violation	2	(0.0)	2	(0.0)	4	(0.0)
Withdrawal By Subject	265	(4.3)	273	(4.5)	538	(4.4)
Protocol Milestone						
Continuing Into Next Trial Segment	5,177	(84.8)	5,176	(84.5)	10,353	(84.7)
Not Continuing Into Next Trial Segment	305	(5.0)	334	(5.5)	639	(5.2)
Unknown	620	(10.2)	614	(10.0)	1,234	(10.1)
Each subject is counted once for Trial Disposition, Protocol Milestone based on the latest corresponding disposition record. Unknown: A disposition record did not exist at the time of reporting.						

Table 5. Disposition of Subjects (> Month 42 to Month 48) (All Randomized Subjects, Efficacy Substudy)

	9vHPV Vaccine		qHPV Vaccine		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	3,493		3,552		7,045	
Trial Disposition						
Completed	3,455	(98.9)	3,528	(99.3)	6,983	(99.1)
Discontinued	38	(1.1)	24	(0.7)	62	(0.9)
Adverse Event	1	(0.0)	1	(0.0)	2	(0.0)
Lost To Follow-Up	7	(0.2)	5	(0.1)	12	(0.2)
Pregnancy	0	(0.0)	1	(0.0)	1	(0.0)
Withdrawal By Subject	30	(0.9)	17	(0.5)	47	(0.7)
Protocol Milestone						
Continuing Into Next Trial Segment	3,430	(98.2)	3,519	(99.1)	6,949	(98.6)
Not Continuing Into Next Trial Segment	26	(0.7)	9	(0.3)	35	(0.5)
Unknown	37	(1.1)	24	(0.7)	61	(0.9)
Each subject is counted once for Trial Disposition, Protocol Milestone based on the latest corresponding disposition record. Unknown: A disposition record did not exist at the time of reporting.						

Table 6. Disposition of Subjects (> Month 48 to Month 54) (All Randomized Subjects, Efficacy Substudy)

	9vHPV Vaccine		qHPV Vaccine		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	788		818		1,606	
Trial Disposition						
Completed	783	(99.4)	813	(99.4)	1,596	(99.4)
Discontinued	5	(0.6)	5	(0.6)	10	(0.6)
Lost To Follow-Up	0	(0.0)	3	(0.4)	3	(0.2)
Withdrawal By Subject	5	(0.6)	2	(0.2)	7	(0.4)
Protocol Milestone						
Continuing Into Next Trial Segment	300	(38.1)	310	(37.9)	610	(38.0)
Not Continuing Into Next Trial Segment	483	(61.3)	504	(61.6)	987	(61.5)
Unknown	5	(0.6)	4	(0.5)	9	(0.6)
Each subject is counted once for Trial Disposition, Protocol Milestone based on the latest corresponding disposition record.						
Unknown: A disposition record did not exist at the time of reporting.						

The study was to be terminated when 30 cases had been retrieved and continued follow- up until month 42 for remaining subjects. This appears to be the explanation for the lower number of subjects in the two last follow-up periods.

Study 002

A total of 3111 subjects were screened for inclusion in this study, 3074 were randomized, and 3066 received at least 1 vaccination. A summary of the number of subjects who were randomized, vaccinated, who completed or discontinued during the study, by vaccination group, is provided in the table below.

Table 7. Disposition of Subjects (All Randomized Subjects)

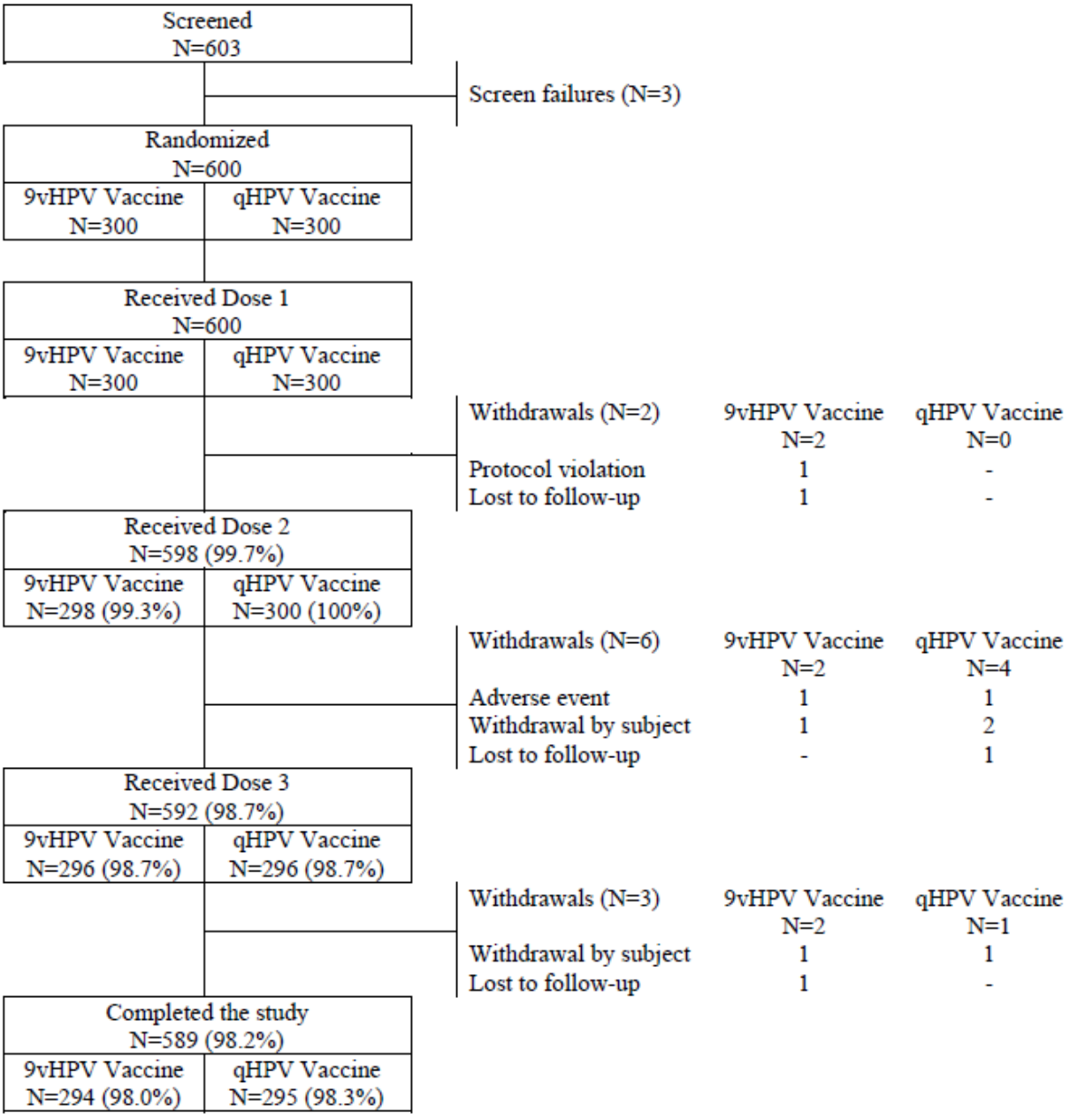
	9- to 15-Year-Old Females (Lot 1)		9- to 15-Year-Old Females (Lot 2)		9- to 15-Year-Old Females (Lot 3)		9- to 15-Year-Old Males		16- to 26-Year-Old Females		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	648		643		644		669		470		3,074	
Vaccinated at												
Vaccination 1	646	(99.7)	642	(99.8)	644	(100.0)	666	(99.6)	468	(99.6)	3,066	(99.7)
Vaccination 2	637	(98.3)	633	(98.4)	638	(99.1)	658	(98.4)	462	(98.3)	3,028	(98.5)
Vaccination 3	635	(98.0)	627	(97.5)	637	(98.9)	653	(97.6)	455	(96.8)	3,007	(97.8)
Study Disposition												
COMPLETED	623	(96.1)	621	(96.6)	631	(98.0)	647	(96.7)	444	(94.5)	2,966	(96.5)
DISCONTINUED	25	(3.9)	22	(3.4)	13	(2.0)	22	(3.3)	22	(4.7)	104	(3.4)
ADVERSE EVENT	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.0)
LOST TO FOLLOW-UP	12	(1.9)	8	(1.2)	10	(1.6)	8	(1.2)	11	(2.3)	49	(1.6)
PHYSICIAN DECISION	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	2	(0.1)
PREGNANCY	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.0)
PROTOCOL VIOLATION	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)	2	(0.4)	3	(0.1)
WITHDRAWAL BY SUBJECT	12	(1.9)	13	(2.0)	2	(0.3)	13	(1.9)	8	(1.7)	48	(1.6)
UNKNOWN	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	4	(0.9)	4	(0.1)

There are no major differences between the groups, and no striking discontinuations.

Study 009/GDS01C

A total of 603 subjects entered the study between 23 February 2011 and 11 May 2011. A flow-chart of the number of subjects at each stage of the study is given below.

Figure 1. Flow-Chart of Subjects Participation



The number of subjects completing the study was high, and similar between the two groups.

Recruitment

Study 001

The first subject received the first dose on September 26, 2007, and the last subject received the third dose on October 3, 2011. Subjects were followed for efficacy through at least month 42. Further follow-up is planned.

Study 002

The first subject received the first dose on August 27, 2009, and the last subject received the third dose on August 18, 2011. Subjects were initially planned to be followed until Month 12, but the study was extended through month 36.

Study 009/GDS01C

The first visit for the first subject was February 23, 2011, and the last visit of the last subject was December 20, 2011. The subjects were followed through month 7, i.e. 1 month after the last vaccination.

Baseline data

Study 001

Table 7 displays the demographic characteristics of subjects randomized into the dose-ranging substudy, by vaccination group. Table 8 displays the demographic characteristics of subjects randomized into the efficacy substudy, by vaccination group.

Pap tests were obtained in all subjects at Day 1. An abnormal Pap test at Day 1 was not a reason for exclusion from the study, and the results of this test were not part of the criteria to define the per protocol populations. Nonetheless, the results of this screening, which was mandated by the protocol, provided a general estimate of the burden of HPV-related cervical disease at enrolment. Table 9 displays the Pap test results at Day 1 for all randomized subjects in the efficacy substudy by vaccination group.

HPV serostatus and HPV PCR status was tested in all subjects at Day 1 for all HPV vaccine types. Seropositivity and/or PCR positivity at Day 1 were not a reason for exclusion from the study. However, the results of this screening were part of the criteria to define the PPI and PPE populations for each vaccine HPV type. A subject was defined to be anti-HPV 6, anti-HPV 11, anti-HPV 16, anti-HPV 18, anti-HPV-31, anit-HPV-33, anti-HPV 45, anti-HPV 52, or anti-HPV 58 seropositive to HPV Types 6, 11, 16, 18, 31, 33, 45, 52, or 58, respectively, if her anti-HPV serum cLIA level was greater than or equal to the established cut off defined for the specific HPV type. A subject was defined to be HPV DNA positive if at least one cervico-vaginal specimen was found to be positive for HPV 6, 11, 16, 18, 31, 33, 45, 52, and/or 58 by PCR. Table 10 summarize the composite HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 status by PCR and/or serology at Day 1 by vaccination group in the efficacy substudy. There were regional variations in the composite HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 status by PCR and/or serology at Day 1. In Latin America, the number of subjects positive to at least one of the 9 HPV types by serology, by PCR, and by serology and PCR was higher than subjects in the other regions. Fewer subjects in the Asia-Pacific region were positive to at least one of the 9 HPV types by PCR than subjects in the other regions**.**

Table 8. Subject Characteristics (All Randomized Subjects, Dose-Ranging Substudy)

	Low-Dose 9vHPV Vaccine		Mid-Dose 9vHPV Vaccine		High-Dose 9vHPV Vaccine		qHPV Vaccine		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	315		307		310		310		1,242	
Gender										
Female	315	(100.0)	307	(100.0)	310	(100.0)	310	(100.0)	1,242	(100.0)
Age (Years)										
15 and under	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
16 to 18	23	(7.3)	31	(10.1)	20	(6.5)	34	(11.0)	108	(8.7)
19 to 21	120	(38.1)	102	(33.2)	120	(38.7)	95	(30.6)	437	(35.2)
22 to 24	125	(39.7)	113	(36.8)	112	(36.1)	124	(40.0)	474	(38.2)
25 to 26	47	(14.9)	61	(19.9)	58	(18.7)	57	(18.4)	223	(18.0)
27 and above	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Mean	21.7		22.0		21.9		21.9		21.9	
SD	2.4		2.5		2.4		2.5		2.4	
Median	22.0		22.0		22.0		22.0		22.0	
Range	16 to 26		16 to 26		16 to 26		16 to 26		16 to 26	
Race										
American Indian Or Alaska Native	0	(0.0)	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.1)
Asian	40	(12.7)	37	(12.1)	36	(11.6)	40	(12.9)	153	(12.3)
Black Or African American	18	(5.7)	10	(3.3)	14	(4.5)	14	(4.5)	56	(4.5)
Multi-Racial	92	(29.2)	99	(32.2)	98	(31.6)	101	(32.6)	390	(31.4)
Native Hawaiian Or Other Pacific Islander	0	(0.0)	1	(0.3)	1	(0.3)	2	(0.6)	4	(0.3)
Unknown	1	(0.3)	1	(0.3)	0	(0.0)	0	(0.0)	2	(0.2)
White	164	(52.1)	159	(51.8)	160	(51.6)	153	(49.4)	636	(51.2)
Ethnicity										
Hispanic Or Latino	125	(39.7)	127	(41.4)	117	(37.7)	125	(40.3)	494	(39.8)
Not Hispanic Or Latino	190	(60.3)	180	(58.6)	193	(62.3)	185	(59.7)	748	(60.2)
Region										
Asia-Pacific	34	(10.8)	32	(10.4)	35	(11.3)	34	(11.0)	135	(10.9)
Europe	58	(18.4)	58	(18.9)	57	(18.4)	57	(18.4)	230	(18.5)
Latin America	114	(36.2)	113	(36.8)	112	(36.1)	115	(37.1)	454	(36.6)
North America	109	(34.6)	104	(33.9)	106	(34.2)	104	(33.5)	423	(34.1)
Smoking Status										
Current smoker	53	(16.8)	46	(15.0)	50	(16.1)	46	(14.8)	195	(15.7)
Ex-smoker	21	(6.7)	25	(8.1)	24	(7.7)	18	(5.8)	88	(7.1)
Never smoked	240	(76.2)	236	(76.9)	235	(75.8)	246	(79.4)	957	(77.1)
Unknown	1	(0.3)	0	(0.0)	1	(0.3)	0	(0.0)	2	(0.2)

Table 9. Subject Characteristics (All Randomized Subjects, Efficacy Substudy)

	9vHPV Vaccine		qHPV Vaccine		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	7,106		7,109		14,215	
Gender						
Female	7,106	(100.0)	7,109	(100.0)	14,215	(100.0)
Age (Years)						
15 and under	0	(0.0)	0	(0.0)	0	(0.0)
16 to 18	674	(9.5)	747	(10.5)	1,421	(10.0)
19 to 21	2,489	(35.0)	2,437	(34.3)	4,926	(34.7)
22 to 24	2,666	(37.5)	2,701	(38.0)	5,367	(37.8)
25 to 26	1,277	(18.0)	1,224	(17.2)	2,501	(17.6)
27 and above	0	(0.0)	0	(0.0)	0	(0.0)
Mean	21.9		21.8		21.9	
SD	2.5		2.5		2.5	
Median	22.0		22.0		22.0	
Range	16 to 26		16 to 26		16 to 26	
Race						
American Indian Or Alaska Native	6	(0.1)	10	(0.1)	16	(0.1)
Asian	1,022	(14.4)	1,006	(14.2)	2,028	(14.3)
Black Or African American	243	(3.4)	233	(3.3)	476	(3.3)
Multi-Racial	1,897	(26.7)	1,909	(26.9)	3,806	(26.8)
Native Hawaiian Or Other Pacific Islander	5	(0.1)	10	(0.1)	15	(0.1)
Unknown	10	(0.1)	13	(0.2)	23	(0.2)
White	3,923	(55.2)	3,928	(55.3)	7,851	(55.2)
Ethnicity						
Hispanic Or Latino	2,525	(35.5)	2,510	(35.3)	5,035	(35.4)
Not Hispanic Or Latino	4,580	(64.5)	4,599	(64.7)	9,179	(64.6)
NULL	1	(0.0)	0	(0.0)	1	(0.0)
Region						
Asia-Pacific	905	(12.7)	909	(12.8)	1,814	(12.8)
Europe	2,406	(33.9)	2,409	(33.9)	4,815	(33.9)
Latin America	2,372	(33.4)	2,372	(33.4)	4,744	(33.4)
North America	1,423	(20.0)	1,419	(20.0)	2,842	(20.0)
Smoking Status						
Current smoker	1,071	(15.1)	1,005	(14.1)	2,076	(14.6)
Ex-smoker	382	(5.4)	358	(5.0)	740	(5.2)
Never smoked	5,647	(79.5)	5,744	(80.8)	11,391	(80.1)
Unknown	6	(0.1)	2	(0.0)	8	(0.1)

Table 10. Summary of Pap Test Results at Day 1 by Vaccination Group (All Randomized Subjects, Efficacy Substudy)

	9vHPV Vaccine (N=7,106)		qHPV Vaccine (N=7,109)		Total (N=14,215)	
	n	(%)	n	(%)	n	(%)
Subjects with Day 1 Pap test result	7,068		7,076		14,144	
Day 1 Pap test result †						
Unsatisfactory	35	(0.5)	37	(0.5)	72	(0.5)
Satisfactory	7,033	(99.5)	7,039	(99.5)	14,072	(99.5)
Day 1 Pap test diagnosis ‡						
Negative for SIL	6,198	(88.1)	6,202	(88.1)	12,400	(88.1)
Negative	6,179	(87.9)	6,181	(87.8)	12,360	(87.8)
Reactive/reparative	19	(0.3)	21	(0.3)	40	(0.3)
Borderline Abnormal Pap						
ASC-US (LR and HR-HPV unknown)	9	(0.1)	7	(0.1)	16	(0.1)
ASC-US (LR and HR-HPV negative)	93	(1.3)	97	(1.4)	190	(1.4)
ASC-US (LR positive and HR negative)	22	(0.3)	11	(0.2)	33	(0.2)
Abnormal Pap						
ASC-US (HR positive), LSIL, or worse	712	(10.1)	722	(10.3)	1,434	(10.2)
ASC-US (HR positive)	163	(2.3)	193	(2.7)	356	(2.5)
LSIL	509	(7.2)	490	(7.0)	999	(7.1)
ASC-H	7	(0.1)	18	(0.3)	25	(0.2)
HSIL	31	(0.4)	21	(0.3)	52	(0.4)
Atypical glandular cells	1	(0.0)	0	(0.0)	1	(0.0)
Squamous cell carcinoma	1	(0.0)	0	(0.0)	1	(0.0)

† Percentages for satisfactory/unsatisfactory calculated as 100*(n/number of subjects with Day 1 Pap test result).

‡ Percentages for Pap test diagnoses calculated as 100*(n/number of subjects with satisfactory Pap test result).

N = Number of subjects randomized.

n = Number of subjects who have the indicated diagnosis or Pap test result.

ASC-H = Atypical squamous cells, cannot exclude HSIL; ASC-US = Atypical squamous cells of undetermined significance;

HPV = Human papillomavirous; HR = High risk HPV probe result; HSIL = High-grade squamous intraepithelial lesion; LR = Low risk HPV probe result; LSIL = Low-grade squamous intraepithelial lesion; Pap = Papanicolaou's test.

Table 11. Summary of Composite HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 Status by PCR and/or Serology at Day 1 by Vaccination Group (All Randomized Subjects, Efficacy Substudy)

Day 1 Composite HPV 6/11/16/18/31/33/45/52/58 Status	9vHPV Vaccine (N=7,106) m/n (%)		qHPV Vaccine (N=7,109) m/n (%)		Total (N=14,215) m/n (%)	
Negative to HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58						
By serology	4,311/7,082	(60.9)	4,431/7,078	(62.6)	8,742/14,160	(61.7)
By PCR	5,032/6,919	(72.7)	5,023/6,943	(72.3)	10,055/13,862	(72.5)
By serology and PCR	3,605/6,970	(51.7)	3,638/6,983	(52.1)	7,243/13,953	(51.9)
Positive to HPV 6, 11, 16, 18, 31, 33, 45, 52 or 58						
By serology	2,771/7,082	(39.1)	2,647/7,078	(37.4)	5,418/14,160	(38.3)
By PCR	1,887/6,919	(27.3)	1,920/6,943	(27.7)	3,807/13,862	(27.5)
By serology or PCR	3,365/6,970	(48.3)	3,345/6,983	(47.9)	6,710/13,953	(48.1)

Percentages are calculated as 100*(m/n).
Positive (Negative) by serology is defined as having an anti-HPV cLIA titer ≥ (<) the serostatus cutoff values of 30, 16, 20, 24, 10, 8, 8, 8 and 8 milli Merck Units/mL, respectively, for HPV-types 6, 11, 16 18, 31, 33, 45, 52 and 58.
N = Number of subjects randomized.
m = Number of subjects in the respective category.
n = Number of subjects with non-missing data (serology, PCR, or both) at Day 1 for HPV-types 6, 11, 16, 18, 31, 33, 45, 52 and 58.
cLIA = Competitive Luminex immunoassay; HPV = Human papillomavirus; PCR = Polymerase chain reaction.

Study 002

Table 11 displays the demographic characteristics of subjects randomized into this study, by vaccination group. The demographic characteristics of subjects who are in the PPI population for at least one HPV type were generally comparable with those of the all-randomized subject population.

As in study 001 Pap tests were obtained in all 16- to 26-year-old females at Day 1. Table 12 displays the Pap test results at Day 1 for all randomized 16- to 26-year-old females.

Table 12. Subject Characteristics (All Randomized Subjects)

	9- to 15-Year-Old Females (Lot 1)		9- to 15-Year-Old Females (Lot 2)		9- to 15-Year-Old Females (Lot 3)		9- to 15-Year-Old Males		16- to 26-Year-Old Females		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	648		643		644		669		470		3,074	
Gender												
Male	0	(0.0)	0	(0.0)	0	(0.0)	669	(100.0)	0	(0.0)	669	(21.8)
Female	648	(100.0)	643	(100.0)	644	(100.0)	0	(0.0)	470	(100.0)	2,405	(78.2)
Age (Years)												
9 to 12 Years of Age	440	(67.9)	432	(67.2)	432	(67.1)	450	(67.3)	0	(0.0)	1,754	(57.1)
13 to 15 Years of Age	208	(32.1)	211	(32.8)	212	(32.9)	219	(32.7)	0	(0.0)	850	(27.7)
16 to 26 Years of Age	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	470	(100.0)	470	(15.3)
Mean	11.7		11.6		11.6		11.7		21.3		13.1	
SD	1.8		1.8		1.9		1.8		2.7		4.0	
Median	12.0		11.0		11.0		12.0		21.0		12.0	
Range	9 to 15		9 to 15		9 to 15		9 to 15		16 to 26		9 to 26	
Race												
American Indian Or Alaska Native	1	(0.2)	1	(0.2)	0	(0.0)	2	(0.3)	0	(0.0)	4	(0.1)
Asian	150	(23.1)	141	(21.9)	139	(21.6)	186	(27.8)	128	(27.2)	744	(24.2)
Black Or African American	50	(7.7)	59	(9.2)	52	(8.1)	37	(5.5)	48	(10.2)	246	(8.0)
Multi-Racial	81	(12.5)	91	(14.2)	86	(13.4)	149	(22.3)	53	(11.3)	460	(15.0)
Native Hawaiian Or Other Pacific Islander	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.4)	1	(0.2)	4	(0.1)
White	366	(56.5)	351	(54.6)	367	(57.0)	292	(43.6)	240	(51.1)	1,616	(52.6)
Ethnicity												
Hispanic Or Latino	176	(27.2)	191	(29.7)	193	(30.0)	195	(29.1)	128	(27.2)	883	(28.7)
Not Hispanic Or Latino	472	(72.8)	452	(70.3)	451	(70.0)	474	(70.9)	342	(72.8)	2,191	(71.3)
Weight												
Subjects with data	648		643		644		669		468		3072	
Mean	45.4		45.3		45.1		45.4		60.0		47.5	
SD	13.2		14.1		13.6		15.1		13.1		14.9	
Median	43.5		43.3		43.5		42.0		58.0		45.8	
Range	19.5 to 132.0		18.0 to 109.3		20.0 to 152.0		15.4 to 115.2		35.0 to 126.1		15.4 to 152.0	
Body Mass Index												
Subjects with data	647		643		644		669		468		3071	
Mean	19.7		19.7		20.0		19.6		22.6		20.2	
SD	4.4		4.3		4.5		4.2		4.6		4.5	
Median	18.9		18.8		19.2		18.6		21.6		19.3	
Range	11.1 to 58.8		5.6 to 46.4		10.5 to 57.5		10.1 to 43.0		15.4 to 47.5		5.6 to 58.8	
Region												
Africa	32	(4.9)	34	(5.3)	29	(4.5)	30	(4.5)	40	(8.5)	165	(5.4)
Asia-Pacific	148	(22.8)	137	(21.3)	138	(21.4)	185	(27.7)	125	(26.6)	733	(23.8)
Europe	206	(31.8)	182	(28.3)	185	(28.7)	143	(21.4)	183	(38.9)	899	(29.2)
Latin America	125	(19.3)	147	(22.9)	136	(21.1)	160	(23.9)	60	(12.8)	628	(20.4)
North America	137	(21.1)	143	(22.2)	156	(24.2)	151	(22.6)	62	(13.2)	649	(21.1)
Smoking Status												
Current smoker	3	(0.5)	2	(0.3)	4	(0.6)	4	(0.6)	61	(13.0)	74	(2.4)
Ex-smoker	2	(0.3)	1	(0.2)	2	(0.3)	3	(0.4)	28	(6.0)	36	(1.2)
Never smoked	643	(99.2)	640	(99.5)	638	(99.1)	662	(99.0)	379	(80.6)	2,962	(96.4)
Unknown	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.4)	2	(0.1)

Table 13. Summary of Pap Test Results at Day 1 by Vaccination Group (16- to 26- Year-Old Females Only) (All Randomized Subjects)

	16- to 26-Year-Old Females (N=470)	
	n	(%)
Subjects with Day 1 Pap test result	458	
Day 1 Pap test result †		
Unsatisfactory	3	(0.7)
Satisfactory	455	(99.3)
Day 1 Pap test diagnosis ‡		
Negative for SIL	399	(87.7)
Negative	394	(86.6)
Reactive/reparative	5	(1.1)
Borderline Abnormal Pap		
ASC-US (LR and HR-HPV unknown)	1	(0.2)
ASC-US (LR and HR-HPV negative)	6	(1.3)
Abnormal Pap		
ASC-US (HR positive), LSIL, or worse	49	(10.8)
ASC-US (HR positive)	16	(3.5)
LSIL	32	(7.0)
HSIL	1	(0.2)

† Percentages for satisfactory/unsatisfactory calculated as 100*(n/number of subjects with Day 1 Pap test result).

‡ Percentages for Pap test diagnoses calculated as 100*(n/number of subjects with satisfactory Pap test result).

N = Number of subjects randomized.

n = Number of subjects who have the indicated diagnosis or Pap test result.

ASC-US = Atypical squamous cells of undetermined significance;

HPV = Human papillomavirous; HR = High risk HPV probe result; HSIL = High-grade squamous intraepithelial lesion; LR = Low risk HPV probe result; LSIL = Low-grade squamous intraepithelial lesion; Pap = Papanicolaou's test.

Table 14. Summary of Composite HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 Status by PCR and/or Serology at Day 1 in 16- to 26-Year-Old Females by Vaccination Group (All Randomized Subjects)

Day 1 Composite HPV 6/11/16/18/31/33/45/52/58 Status	16- to 26-Year-Old Females (N=470) m/n (%)	
Negative to HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58		
By serology	315/466	(67.6)
By PCR	341/441	(77.3)
By serology and PCR	266/450	(59.1)
Positive to HPV 6, 11, 16, 18, 31, 33, 45, 52 or 58		
By serology	151/466	(32.4)
By PCR	100/441	(22.7)
By serology or PCR	184/450	(40.9)

Percentages are calculated as 100*(m/n).

Positive (Negative) by serology is defined as having an anti-HPV cLIA titer ≥ (<) the serostatus cutoff values of 30, 16, 20, 24, 10, 8, 8, 8 and 8 milli Merck Units/mL, respectively, for HPV-types 6, 11, 16 18, 31, 33, 45, 52 and 58

N = Number of subjects randomized.

m = Number of subjects in the respective category.

n = Number of subjects with non-missing data (serology, PCR, or both) at Day 1 for HPV-types 6, 11, 16, 18, 31, 33, 45, 52 and 58.

cLIA = Competitive Luminex immunoassay; HPV = Human papillomavirus; PCR = Polymerase chain reaction.

Study 009/GDS01C

Table 14 summarises the demographic characteristics at baseline for the subjects randomized in the study. Results on the Per Protocol Sets were comparable to the results on the Randomized Set.

Table 15. Summary of Demographic Characteristics – Randomized Set

	9vHPV Vaccine (N=300)	qHPV Vaccine (N=300)	All (N=600)
Gender			
Female n (%)	300 (100%)	300 (100%)	600 (100%)
Age (years) at first dose			
Mean (SD)	12.6 (1.9)	12.6 (1.9)	12.6 (1.9)
Min. ; Max.	9.0 ; 16.0	9.0 ; 16.0	9.0 ; 16.0
9 to 12 years old	n=150	n=150	n=300
Mean (SD)	10.9 (1.0)	11.0 (1.0)	11.0 (1.0)
13 to 15 years old	n=150	n=150	n=300
Mean (SD)	14.3 (0.8)	14.3 (0.8)	14.3 (0.8)
Race			
Black	1 (0.3%)	1 (0.3%)	2 (0.3%)
White	296 (98.7%)	294 (98.0%)	590 (98.3%)
Asian	0 (0%)	1 (0.3%)	1 (0.2%)
Multi racial	3 (1.0%)	4 (1.3%)	7 (1.2%)
Weight (kg)			
Mean (SD)	48.1 (12.6)	47.4 (11.5)	47.8 (12.1)
Min. ; Max.	25 ; 94	25 ; 82	25 ; 94
Height (cm)			
Mean (SD)	154.6 (10.9)	155.0 (10.6)	154.8 (10.7)
Min. ; Max.	129 ; 176	116 ; 176	116 ; 176
Region			
Europe n (%)	300 (100%)	300 (100%)	600 (100%)
Smoking status			
Current smoker	1 (0.3%)	3 (1.0%)	4 (0.7%)
Ex-smoker	1 (0.3%)	0 (0%)	1 (0.2%)
Never smoked	298 (99.3%)	297 (99.0%)	595 (99.2%)

SD: standard deviation

Baseline HPV serostatus is summarized in Table 15.

Table 16. Baseline HPV status – Randomized Set

	9vHPV Vaccine (N=300)	qHPV Vaccine (N=300)	All (N=600)
	n (%)	n (%)	n (%)
Seronegative for HPV type 6	296 (98.7%)	291 (97.0%)	587 (97.8%)
Seronegative for HPV type 11	298 (99.3%)	298 (99.3%)	596 (99.3%)
Seronegative for HPV type 16	299 (99.7%)	299 (99.7%)	598 (99.7%)
Seronegative for HPV type 18	299 (99.7%)	298 (99.3%)	597 (99.5%)
Seronegative for HPV type 31	300 (100%)	296 (98.7%)	596 (99.3%)
Seronegative for HPV type 33	298 (99.3%)	298 (99.3%)	596 (99.3%)
Seronegative for HPV type 45	299 (99.7%)	300 (100%)	599 (99.8%)
Seronegative for HPV type 52	299 (99.7%)	298 (99.3%)	597 (99.5%)
Seronegative for HPV type 58	291 (97.0%)	289 (96.3%)	580 (96.7%)
All other subjects were seropositive at baseline (no missing data)			

Numbers analysed

Study 001

Dose-ranging substudy –The primary analysis population was the PPI population. A total of 1239 subjects received at least one dose of vaccine. A total of 789 (HPV 6), 789 (HPV 11), 798 (HPV 16), 903 (HPV 18), 862 (HPV 31), 923 (HPV 33), 930 (HPV 45), 840 (HPV 52), and 886 (HPV 58) subjects, respectively representing 63.7%, 637.7%, 64.4%, 72.9% 69.6%, %, 74.5%, 75.1%, 67,8% and 71.5% of the entire study population were eligible to be included in the PPI analysis. The most common reasons subjects were excluded from the PPI population were:

- Being positive to a vaccine HPV type at or prior to Month 7:

  HPV types 6 and 11 L1 proteins are highly homologous, resulting in strong cross-reactivity between the 2 types. Therefore, subjects positive for HPV Type 6 were also excluded from the analysis for HPV Type 11, and vice versa. This approach to defining the HPV 6- and HPV 11- per protocol populations is applied to both the immunogenicity and efficacy per-protocol analysis populations, and is consistent with the approach previously used in the qHPV vaccine clinical program.

- Missing Month 7 serology samples/results
- Missing Day 1 or Month 7 swab samples/results
- Incomplete vaccinations or vaccinations done out of range
- General protocol violations

Immunogenicity substudy – The primary analysis population was the PPI population. A total of 13587 subjects received at least one dose of 9vHPV or qHPV. A total of 7968 (HPV 6), 7977 (HPV 11), 8094 (HPV 16), 9080 (HPV 18), 8843 (HPV 31), 9393 (HPV 33), 9542 (HPV 45), 8790 (HPV 52), and 8932 (HPV 58) subjects, respectively representing 58.6%, 58.7%, 59.6%, 66.8% , 65.1%, 69,1%, 70.2%, 64.7%, and 65.8% of the entire study population were eligible to be included in the PPI analysis for these HPV types. The most common reasons subjects were excluded from the PPI population were the same as in the dose ranging PPI population described above.

Efficacy substudy –The primary analysis population for analysis of efficacy was the PPE population. A total of 10,735 (HPV 31), 11,444 (HPV 33), 11,638 (HPV 45), 10,719 (HPV 52), and 10,888 (HPV 58) subjects, representing 75.5%, 80.5%, 81.9%, 75.4%, and 76.6% of the entire study population were eligible to be included in the PPE analysis for these HPV types. The numbers of subjects who were eligible for each endpoint for each HPV type were similar between the 9vHPV vaccine and qHPV vaccine groups. The most common reasons for excluding subjects from the PPE population were the same as for the dose-ranging and immunogenicity populations above.

A total of 10,735 (HPV 31), 11,444 (HPV 33), 11,638 (HPV 45), 10,719 (HPV 52), and 10,888 (HPV 58) subjects, representing 75.5%, 80.5%, 81.9%, 75.4%, and 76.6% of the entire study population had disease and persistent infection follow-up after Month 7 and were eligible to be included in the PPE analysis for these HPV types. The numbers of subjects who were eligible for each endpoint for each HPV type were similar between the 9vHPV vaccine and qHPV vaccine groups.

Study 002

The primary analysis population was the PPI population. A total of 3066 subjects received at least one dose of vaccine. . A total of 2521 (HPV 31), 2558(HPV 33), 2585 (HPV 45), 2547 (HPV 52), and 2528 (HPV 58) subjects, representing 82.2%, %, 83.4%, 84.3%, 83.0% and 82.5% of the entire study population were eligible to be included in the PPI analysis for these HPV types. The most common reasons subjects were excluded from the PPI population were:

- Being positive to a vaccine HPV type at or prior to Month 7:
    - HPV types 6 and 11 L1 proteins are highly homologous, resulting in strong cross-reactivity between the 2 types. Therefore, subjects positive for HPV Type 6 were also excluded from the analysis for HPV Type 11, and vice versa. This approach to defining the HPV 6- and HPV 11- per protocol populations is applied to both the immunogenicity and efficacy per-protocol analysis populations, and is consistent with the approach previously used in the qHPV vaccine clinical program.
- Missing Month 7 serology samples/results
- Missing Day 1 or Month 7 swab samples/results
- Received non-study vaccination
- Incomplete vaccinations or vaccinations done out of range

Study 009/GDS01C

The Per Protocol set (PPS) included 547 subjects (91.2%): 276 subjects receiving 9vHPV vaccine and 271 receiving qHPV vaccine. The HPV type-specific PPS included from 528 subjects (88.0%) for HPV 58 to 546 subjects (91.0%) for HPV 16 and HPV 45. The most common reasons for exclusion from the PPS were:

- pre-vaccination seropositivity
- Non compliance with blood sample requirements
- Non compliance with vaccination schedule
- General protocol deviations

Overall, the most common reason for excluding subjects from the per protocol populations for Immunogenicity or efficacy was seropositivity for at least one of the HPV types. This was higher in study 001 than in the other studies, which is not unexpected considering the higher mean age in 001 compared to the other two studies. Overall, the numbers excluded are reasonable, and do not cause concern.

Outcomes and estimation

Study 001

Efficacy results - HPV 31/33/45/52/58-Related Endpoints

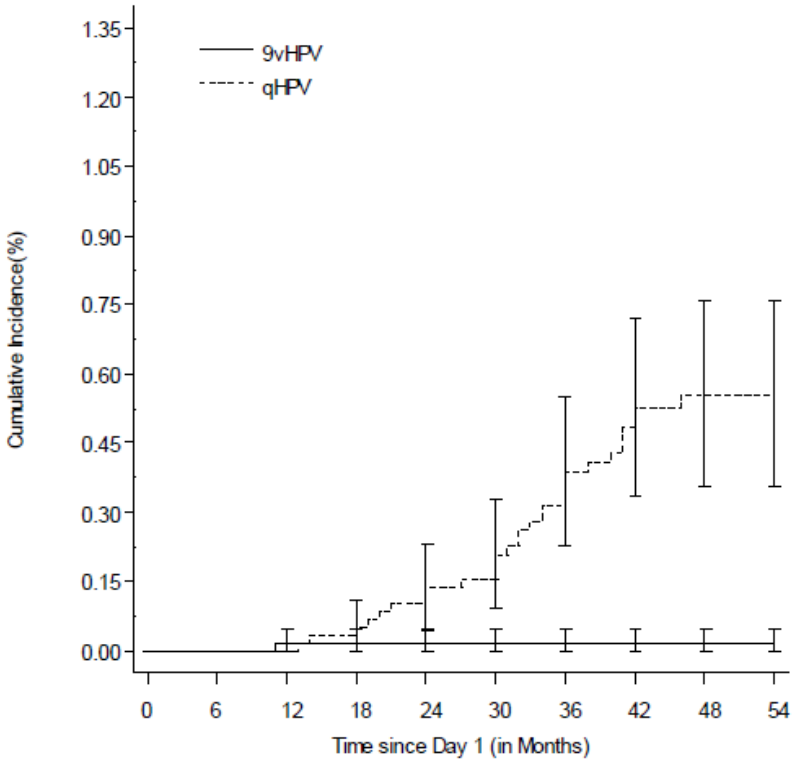
Table 16 presents the results of evaluation of efficacy against the primary efficacy endpoint of high grade cervical, vulvar, and vaginal disease related to HPV types 31, 33, 45, 52, and 58 in the PPE population with a median follow-up of 40 months post dose 3. The point estimate of vaccine efficacy is statistically significant. The success criterion as pre-specified in the study protocol, i.e. that lower bound of the 95% confidence interval (CI) of vaccine efficacy (VE) be greater than 25%, has been met. The cumulative incidence distribution of the primary efficacy endpoint in the PPE population is shown in Figure 2.

Table 17. Analysis of Efficacy Against HPV 31/33/45/52/58-Related CIN 2/3, AIS, Cervical Cancer, VIN 2/3, VaIN 2/3, Vulvar Cancer, and Vaginal Cancer – median follow-up of 40 months post dose 3 (Per-Protocol Efficacy Analysis Population)

	9vHPV Vaccine (N=7,099)				qHPV Vaccine (N=7,105)						
Endpoint	n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Observed Efficacy (%)	95% CI	P-value[†]
HPV 31/33/45/52/58-Related CIN 2/3, AIS, Cervical Cancer, VIN 2/3, VaIN 2/3, Vulvar Cancer, and Vaginal Cancer	6,016	1	19,005.1	0.0	6,017	30	18,976.6	0.2	96.7	(80.9, 99.8)	< 0.0001
By HPV Type											
HPV 31-Related	5,308	0	16,744.4	0.0	5,252	7	16,560.7	0.0	100	(40.1, 100)	
HPV 33-Related	5,624	0	17,771.4	0.0	5,628	7	17,803.0	0.0	100	(39.3, 100)	
HPV 45-Related	5,724	0	18,102.7	0.0	5,724	2	18,079.2	0.0	100	(-246.8, 100)	
HPV 52-Related	5,320	0	16,777.1	0.0	5,216	11	16,473.6	0.1	100	(67.3, 100)	
HPV 58-Related	5,361	1	16,902.7	0.0	5,340	6	16,842.4	0.0	83.4	(-23.9, 99.3)	
By Lesion Type											
CIN 2 or worse	5,948	1	17,407.0	0.0	5,943	27	17,427.2	0.2	96.3	(79.5, 99.8)	
CIN 2/3 or AIS	5,948	1	17,407.0	0.0	5,943	27	17,427.2	0.2	96.3	(79.5, 99.8)	
CIN 2/3	5,948	1	17,407.0	0.0	5,943	27	17,427.2	0.2	96.3	(79.5, 99.8)	
CIN 2	5,948	1	17,407.0	0.0	5,943	23	17,430.9	0.1	95.6	(76.3, 99.8)	
CIN 3	5,948	0	17,407.0	0.0	5,943	5	17,438.1	0.0	100	(-0.2, 100)	
AIS	5,948	0	17,407.0	0.0	5,943	0	17,441.7	0.0	NA	NA	
Cervical Cancer	5,948	0	17,407.0	0.0	5,943	0	17,441.7	0.0	NA	NA	
VIN 2/3 or VaIN 2/3 or worse	6,009	0	18,976.0	0.0	6,012	3	18,988.0	0.0	100	(-71.5, 100)	
VIN 2/3 or worse	6,009	0	18,976.0	0.0	6,012	0	18,991.0	0.0	NA	NA	
VIN 2/3	6,009	0	18,976.0	0.0	6,012	0	18,991.0	0.0	NA	NA	
Vulvar Cancer	6,009	0	18,976.0	0.0	6,012	0	18,991.0	0.0	NA	NA	
VaIN 2/3 or worse	6,009	0	18,976.0	0.0	6,012	3	18,988.0	0.0	100	(-71.5, 100)	
VaIN 2/3	6,009	0	18,976.0	0.0	6,012	3	18,988.0	0.0	100	(-71.5, 100)	
Vaginal Cancer	6,009	0	18,976.0	0.0	6,012	0	18,991.0	0.0	NA	NA	

[†] P-value calculated for the lower bound of the two sided 95% confidence interval for the vaccine efficacy being greater than 25%.
Subjects are counted once in each applicable endpoint category. A subject may appear in more than one category.
N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects who have at least one follow-up visit after Month 7.
9vHPV = Nine-Valent Human papillomavirus (Types 6, 11, 16, 18, 31, 33, 45, 52, 58) Recombinant Vaccine; qHPV = Quadrivalent Human papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine
AIS = Adenocarcinoma in situ; CI = Confidence interval; CIN = Cervical intraepithelial neoplasia; HPV = Human papillomavirus; NA = Not available (i.e., not calculable); VaIN = Vaginal intraepithelial neoplasia; VIN = Vulvar intraepithelial neoplasia

Figure 2. Time to HPV 31/33/45/52/58-Related CIN 2/3, AIS, Cervical Cancer, VIN 2/3, VaIN 2/3, Vulvar Cancer, and Vaginal Cancer - median follow-up of 40 months post dose 3 (Per-Protocol Efficacy Analysis Population)



Subjects at Risk										
9vHPV	6016	6016	5941	5826	5715	5579	5404	4267	1678	425
qHPV	6017	6017	5926	5816	5698	5572	5400	4294	1708	419
Cumulative Cases										
9vHPV	0	0	1	1	1	1	1	1	1	1
qHPV	0	0	0	3	8	12	22	29	30	30

The single case of the primary efficacy endpoint in the 9vHPV group was a subject who was PCR-negative from Day 1 through the Month 7 study visit for HPV type 58 and hence eligible for inclusion in the HPV 58 PPE analysis; and at the same time was PCR-positive for HPV type 56 starting at Day 1 through Month 42. The subject had a definitive therapy procedure at 4 months after the scheduled Month 7 visit. One of 4 quadrants of the tissue sample obtained during the definitive therapy procedure was diagnosed as a case of CIN 2 by the Pathology Panel and was also PCR-positive for HPV type 58; hence the subject was counted as a case of the primary efficacy endpoint for HPV type 58 at approximately 11 months after vaccination dose 1. Except for the single-time PCR-positive for HPV 58 at Month 11, the subject was PCR-negative for HPV type 58 at all other time points through Month 42.

Table 17 presents the results of evaluation of efficacy against the primary efficacy endpoint of high grade cervical, vulvar, and vaginal disease related to HPV types 31, 33, 45, 52, and 58 in the HNTS population. Consistent with the results in the PPE population, the 9vHPV vaccine is highly efficacious in preventing the incidence of the primary efficacy endpoint among subjects who were naïve to the relevant HPV type at the time of administration of dose 1 of the vaccine. All endpoint cases in the 9vHPV group occurred on or before 18 months after vaccination dose 1.

Among the 6 cases of HPV 31/33/45/52/58-related high grade cervical, vulvar, and vaginal disease in the 9vHPV group in the HNTS population:

- 5 subjects were PCR-positive at Day 1 for at least one oncogenic HPV type other than the HPV type to which the subject became an endpoint case;
- 1 subject was not detected at Day 1 as PCR-positive for any of the oncogenic HPV types tested; was then detected as PCR-positive for multiple oncogenic HPV types at 8 months post Day 1; and was diagnosed as a case HPV 31-related CIN 3 at 10 months post Day 1.

One of the secondary objectives was efficacy against HPV 31/33/45/52/58-Related Cervical, Vulvar, and Vaginal Disease, i.e the same as the primary objective, but also including low-grade disease. The efficacy against this composite endpoint was 97.1% (95% CI 91.9; 99.2).

Table 18. Analysis of Efficacy Against HPV 31/33/45/52/58-Related CIN 2/3, AIS, Cervical Cancer, VIN 2/3, VaIN 2/3, Vulvar Cancer, and Vaginal Cancer - median follow-up of 40 months post dose 3 (HPV-Naive Type-Specific Analysis Population)

	9vHPV Vaccine (N=7,099)				qHPV Vaccine (N=7,105)					
Endpoint	n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Observed Efficacy (%)	95% CI
HPV 31/33/45/52/58-Related CIN 2/3, AIS, Cervical Cancer, VIN 2/3, VaIN 2/3, Vulvar Cancer, and Vaginal Cancer	6,873	6	24,659.4	0.0	6,866	42	24,668.0	0.2	85.7	(68.4, 94.1)
By HPV Type										
HPV 31-Related	6,110	2	21,938.6	0.0	6,104	12	21,917.7	0.1	83.3	(28.0, 97.3)
HPV 33-Related	6,444	1	23,116.3	0.0	6,467	8	23,293.2	0.0	87.4	(19.7, 99.4)
HPV 45-Related	6,562	0	23,549.9	0.0	6,571	3	23,663.4	0.0	100	(-72.3, 100)
HPV 52-Related	6,140	2	22,010.2	0.0	6,129	17	22,063.3	0.1	88.2	(53.7, 98.1)
HPV 58-Related	6,173	1	22,105.8	0.0	6,193	9	22,253.0	0.0	88.8	(19.6, 99.5)
By Lesion Type										
CIN 2 or worse	6,735	5	22,834.7	0.0	6,718	39	22,867.2	0.2	87.2	(67.8, 95.2)
CIN 2/3 or AIS	6,735	5	22,834.7	0.0	6,718	39	22,867.2	0.2	87.2	(67.8, 95.2)
CIN 2/3	6,735	5	22,834.7	0.0	6,718	39	22,867.2	0.2	87.2	(67.8, 95.2)
CIN 2	6,735	4	22,837.0	0.0	6,718	33	22,871.4	0.1	87.9	(67.1, 96.1)
CIN 3	6,735	3	22,834.8	0.0	6,718	9	22,884.6	0.0	66.6	(-22.5, 92.2)
AIS	6,735	0	22,837.5	0.0	6,718	0	22,888.9	0.0	NA	NA
Cervical Cancer	6,735	0	22,837.5	0.0	6,718	0	22,888.9	0.0	NA	NA
VIN 2/3 or VaIN 2/3 or worse	6,870	1	24,633.4	0.0	6,865	3	24,700.5	0.0	66.6	(-203.1, 98.7)
VIN 2/3 or worse	6,870	1	24,633.4	0.0	6,865	0	24,703.5	0.0	NA	NA
VIN 2/3	6,870	1	24,633.4	0.0	6,865	0	24,703.5	0.0	NA	NA
Vulvar Cancer	6,870	0	24,637.2	0.0	6,865	0	24,703.5	0.0	NA	NA
VaIN 2/3 or worse	6,870	0	24,637.2	0.0	6,865	3	24,700.5	0.0	100	(-71.9, 100)
VaIN 2/3	6,870	0	24,637.2	0.0	6,865	3	24,700.5	0.0	100	(-71.9, 100)
Vaginal Cancer	6,870	0	24,637.2	0.0	6,865	0	24,703.5	0.0	NA	NA

Subjects are counted once in each applicable endpoint category. A subject may appear in more than one category.

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.

n = Number of subjects who have at least one follow-up visit after Day 1.

9vHPV = Nine-Valent Human papillomavirus (Types 6, 11, 16, 18, 31, 33, 45, 52, 58) Recombinant Vaccine; qHPV = Quadrivalent Human papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine

AIS = Adenocarcinoma in situ; CI = Confidence interval; CIN = Cervical intraepithelial neoplasia; HPV = Human papillomavirus; NA = Not available (i.e., not calculable); VaIN = Vaginal intraepithelial neoplasia; VIN = Vulvar intraepithelial neoplasia

Table 18 presents the results of evaluation of efficacy against persistent infection related to HPV types 31, 33, 45, 52, and 58 in the PPE and HNTS population. The persistent infection of ≥6 months (±1 month) duration endpoint corresponds to secondary efficacy objective #1. The persistent infection of ≥12 months (±1 month) duration endpoint corresponds to exploratory efficacy objective #1.

Table 19. Analysis of Efficacy Against HPV 31/33/45/52/58-Related Persistent Infection - median follow-up of 40 months post dose 3 (PPE and HN-TS Analysis Populations)

	9vHPV Vaccine (N=7,099)				qHPV Vaccine (N=7,105)						
Analysis Population Endpoint	n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Observed Efficacy (%)	95% CI	P-value[†]
Per-Protocol Efficacy (PPE)											
Persistent Infection ≥6 Months[‡]											
HPV 31/33/45/52/58-Related	5,939	35	16,561.4	0.2	5,953	810	15,451.6	5.2	96.0	(94.4, 97.2)	< 0.0001
HPV 31-Related	5,251	7	14,712.1	0.0	5,198	150	14,316.9	1.0	95.5	(90.7, 97.9)	
HPV 33-Related	5,553	1	15,565.6	0.0	5,560	106	15,416.9	0.7	99.1	(95.2, 100)	
HPV 45-Related	5,649	4	15,809.6	0.0	5,658	124	15,633.4	0.8	96.8	(92.1, 98.9)	
HPV 52-Related	5,263	11	14,737.8	0.1	5,160	387	13,886.7	2.8	97.3	(95.3, 98.7)	
HPV 58-Related	5,297	12	14,831.5	0.1	5,284	225	14,464.9	1.6	94.8	(91.0, 97.1)	
Persistent Infection ≥12 Months[‡]											
HPV 31/33/45/52/58-Related	5,939	21	16,580.5	0.1	5,953	544	15,761.9	3.5	96.3	(94.4, 97.7)	
HPV 31-Related	5,251	4	14,715.9	0.0	5,198	97	14,374.1	0.7	96.0	(89.9, 98.6)	
HPV 33-Related	5,553	1	15,565.6	0.0	5,560	79	15,452.5	0.5	98.7	(93.5, 99.9)	
HPV 45-Related	5,649	2	15,813.2	0.0	5,658	73	15,686.8	0.5	97.3	(90.7, 99.5)	
HPV 52-Related	5,263	7	14,746.0	0.0	5,160	238	14,063.3	1.7	97.2	(94.2, 98.7)	
HPV 58-Related	5,297	7	14,835.1	0.0	5,284	145	14,553.4	1.0	95.3	(90.4, 97.8)	
HPV-Naïve Type-Specific (HN-TS)											
Persistent Infection ≥6 Months[‡]											
HPV 31/33/45/52/58-Related	6,704	148	21,635.5	0.7	6,699	1,150	19,998.4	5.8	88.1	(86.0, 90.0)	
HPV 31-Related	5,971	31	19,558.0	0.2	5,953	234	19,150.7	1.2	87.0	(81.3, 91.4)	
HPV 33-Related	6,281	12	20,579.6	0.1	6,314	152	20,486.1	0.7	92.1	(86.2, 95.7)	
HPV 45-Related	6,395	21	20,911.2	0.1	6,412	170	20,783.2	0.8	87.7	(80.9, 92.3)	
HPV 52-Related	5,991	58	19,545.6	0.3	5,983	552	18,742.8	2.9	89.9	(86.9, 92.4)	
HPV 58-Related	6,020	36	19,675.9	0.2	6,040	324	19,310.6	1.7	89.1	(84.7,	

										92.5)	
Persistent Infection ≥12 Months[‡]											
HPV 31/33/45/52/58-Related	6,704	109	21,708.1	0.5	6,699	802	20,509.3	3.9	87.2	(84.3, 89.6)	
HPV 31-Related	5,971	20	19,581.4	0.1	5,953	159	19,263.8	0.8	87.6	(80.6, 92.6)	
HPV 33-Related	6,281	11	20,580.3	0.1	6,314	109	20,550.3	0.5	89.9	(81.8, 94.9)	
HPV 45-Related	6,395	16	20,920.6	0.1	6,412	101	20,872.3	0.5	84.2	(73.4, 91.3)	
HPV 52-Related	5,991	43	19,577.6	0.2	5,983	356	19,019.7	1.9	88.3	(84.0, 91.7)	
HPV 58-Related	6,020	28	19,683.4	0.1	6,040	218	19,457.9	1.1	87.3	(81.4, 91.8)	

[†] P-value calculated for the lower bound of the two sided 95% confidence interval for the vaccine efficacy being greater than 25%.

[‡] ±1 month visit window.

Subjects are counted once in each applicable endpoint category. A subject may appear in more than one category.

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.

n = Number of subjects in the given population who have at least one follow-up visit after Month 7 in the per-protocol population; after Day 1 in all other analysis populations.

9vHPV = Nine-Valent Human papillomavirus (Types 6, 11, 16, 18, 31, 33, 45, 52, 58) Recombinant Vaccine; qHPV = Quadrivalent Human papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine -- CI = Confidence interval; HPV = Human papillomavirus

The results for the exploratory objectives relating to HPV-31/33/45/52/58-related Pap test abnormalities and cervical and external genital procedures and cervical definitive therapy were in agreement with the above efficacy endpoints. The composite endpoint HPV 31/33/45/52/58 ASC-US HR-HPV positive or worse had a risk reduction of 92.6% (95% CI 89.7; 94.8) in the PP population, and 87.1% (95% CI 84.0, 89.8) in the HNTS population. The risk reduction for HPV 31/33/45/52/58-related biopsy was 96.9% (95% CI 93.6, 98.6) in the PP population and 91.3% (95% CI 87.3, 94.3) in the HNTS population.

In conclusion, the efficacy against the five new HPV types (31/33/45/53/58) was demonstrated using a composite endpoint for all types and CIN 2/3, AIS, Cervical Cancer, VIN 2/3, VaIN 2/3, Vulvar Cancer, and Vaginal Cancer combined. The use of a composite endpoint was discussed in scientific advice previously, and has been considered appropriate. The results are driven by HPV type 52, which was the most common type and CIN2, which was the most common lesion type. The conclusions regarding the primary objective is supported by related secondary objectives. The point estimates for efficacy in the HNTS population were consistently lower, but still considered relevant. The efficacy against milder disease endpoints and persistent infection are also considered supportive of the primary endpoint. Thus, taken together all data relating to the five new HPV types indicate that the 9vHPV is effective in preventing disease related to these types.

Study 001 End of study results

During the procedure for MAA, the Applicant has submitted the final clinical study report for study 001. The main results are briefly described below. The efficacy and safety results were consistent with previous reports.

Table 20. Summary of Efficacy Against HPV 31/33/45/52/58-Related Persistent Infection, Cervical, Vulvar, and Vaginal Disease – median follow-up of 43 months post dose 3 (Per-Protocol Efficacy Analysis Population)

Disease Endpoint	Gardasil 9 N=7099		qHPV Vaccine N=7105		%Efficacy** (95% CI)
	n	Number of cases*	n	Number of cases*	
HPV 31-, 33-, 45-, 52-, 58-related CIN 2/3, AIS, Cervical Cancer, VIN 2/3, VaIN 2/3, Vulvar Cancer, and Vaginal Cancer[α]	6016	1	6017	38	97.4 (85.0, 99.9)
HPV 31-, 33-, 45-, 52-, 58-related CIN 2/3 or AIS[α]	5949	1	5943	35	97.1 (83.5, 99.9)
HPV 31-, 33-, 45-, 52-, 58-related CIN2	5949	1	5943	32	96.9 (81.5, 99.8)
HPV 31-, 33-, 45-, 52-, 58-related CIN3	5949	0	5943	7	100 (39.4, 100)
HPV 31-, 33-, 45-, 52-, 58-related VIN 2/3, VaIN 2/3	6009	0	6012	3	100.0 (-71.5, 100.0)
HPV 31-, 33-, 45-, 52-, 58-related Persistent Infection ≥6 Months[§]	5941	41	5955	946	96.0 (94.6, 97.1)
HPV 31-, 33-, 45-, 52-, 58-related Persistent Infection ≥12 Months[¶]	5941	23	5955	657	96.7 (95.1, 97.9)
HPV 31-, 33-, 45-, 52-, 58-related ASC-US HR-HPV Positive or Worse Pap[#] Abnormality	5883	37	5882	506	92.9 (90.2, 95.1)
HPV 31-, 33-, 45-, 52-, 58-related cervical definitive therapy procedures[†]	6013	4	6014	41	90.2 (75.0, 96.8)

[‡]The PPE population consisted of individuals who received all 3 vaccinations within one year of enrolment, did not have major deviations from the study protocol, were naïve (PCR negative and seronegative) to the relevant HPV type(s) (Types 31, 33, 45,

52, and 58) prior to dose 1, and who remained PCR negative to the relevant HPV type(s) through one month postdose 3 (Month 7).
N=Number of individuals randomized to the respective vaccination group who received at least one injection
n=Number of individuals contributing to the analysis
[§]Persistent infection detected in samples from two or more consecutive visits 6 months (±1 month visit windows) apart.
[¶]Persistent infection detected in samples from three or more consecutive visits 6 months (±1 month visit windows) apart .
[#]Papanicolaou test.
CI=Confidence Interval.
ASC-US=Atypical squamous cells of undetermined significance.
HR=High Risk.
* Number of individuals with at least one follow-up visit after Month 7
** Subjects were followed for up to 54 months postdose 1 (median 4 years)
[¶] no cases of cervical cancer, VIN2/3, vulvar and vaginal cancer were diagnosed in the PPE population
† loop electrosurgical excision procedure (LEEP) or conisation

Over 25% of study subjects completed the Month 54 visit before the end of the study and high vaccine efficacy was maintained up to that time point.

HPV 6/11/16/18-Related Endpoints

It is expected that the 9vHPV vaccine is similarly efficacious in preventing persistent infection and disease related to these four HPV types as the qHPV. Consequently, the risk reduction presented in the following tables 19-21 has no clinical relevance. The comparison of the 9vHPV vaccine group with the qHPV vaccine group with respect to HPV 6/11/16/18-related endpoints is an assessment of similarity of the incidences of these endpoints in the two vaccine groups.

Table 20 presents the results of comparison of the 9vHPV vaccine group with the qHPV vaccine group with respect to cervical, vulvar, and vaginal disease related to HPV types 6, 11, 16, and 18 in the PPE population.

Table 21. Impact of 9vHPV Vaccine on the Incidence of HPV 6/11/16/18-Related Cervical, Vulvar, and Vaginal Disease - median follow-up of 40 months post dose 3 (Per-Protocol Efficacy Analysis Population)

	9vHPV Vaccine (N=7,099)				qHPV Vaccine (N=7,105)					
Endpoint	n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Risk Reduction† (%)	95% CI
HPV 6/11/16/18-Related Cervical, Vulvar, and Vaginal Disease	5,883	6	18,582.5	0.0	5,898	7	18,631.7	0.0	14.1	(-184.8, 71.1)
Cervical Disease	5,823	1	17,059.4	0.0	5,832	3	17,123.4	0.0	66.5	(-203.4, 98.7)
CIN 1	5,823	0	17,059.9	0.0	5,832	2	17,123.4	0.0	100	(-248.5, 100)
CIN 2 or worse	5,823	1	17,059.4	0.0	5,832	1	17,127.2	0.0	-0.4	(≤ -999, 97.4)
Vulvar and Vaginal Disease	5,876	5	18,550.6	0.0	5,893	4	18,615.3	0.0	-25.4	(-394.3, 66.3)
Condyloma	5,876	5	18,550.6	0.0	5,893	1	18,618.7	0.0	-401.8	(≤ -999, 32.6)
VIN 1 or VaIN 1	5,876	0	18,560.3	0.0	5,893	2	18,618.6	0.0	100	(-248.3, 100)
VIN 2/3 or VaIN 2/3 or worse	5,876	0	18,560.3	0.0	5,893	2	18,617.7	0.0	100	(-248.3, 100)
HPV 6/11-Related Cervical, Vulvar, and Vaginal Disease	4,748	4	14,955.4	0.0	4,809	1	15,177.6	0.0	-305.9	(≤ -999, 47.1)
Cervical Disease	4,707	0	13,798.1	0.0	4,759	1	13,976.2	0.0	100	(≤ -999, 100)
CIN 1	4,707	0	13,798.1	0.0	4,759	0	13,976.2	0.0	NA	NA
CIN 2 or worse	4,707	0	13,798.1	0.0	4,759	1	13,976.2	0.0	100	(≤ -999, 100)
Vulvar and Vaginal Disease	4,744	4	14,930.2	0.0	4,805	0	15,161.0	0.0	NA	NA
Condyloma	4,744	4	14,930.2	0.0	4,805	0	15,161.0	0.0	NA	NA
VIN 1 or VaIN 1	4,744	0	14,936.6	0.0	4,805	0	15,161.0	0.0	NA	NA
VIN 2/3 or VaIN 2/3 or worse	4,744	0	14,936.6	0.0	4,805	0	15,161.0	0.0	NA	NA
HPV 6-Related Cervical, Vulvar, and Vaginal Disease	4,748	4	14,955.4	0.0	4,809	1	15,177.6	0.0	-305.9	(≤ -999, 47.1)
Cervical Disease	4,707	0	13,798.1	0.0	4,759	1	13,976.2	0.0	100	(≤ -999, 100)
CIN 1	4,707	0	13,798.1	0.0	4,759	0	13,976.2	0.0	NA	NA
CIN 2 or worse	4,707	0	13,798.1	0.0	4,759	1	13,976.2	0.0	100	(≤ -999, 100)
Vulvar and Vaginal Disease	4,744	4	14,930.2	0.0	4,805	0	15,161.0	0.0	NA	NA
Condyloma	4,744	4	14,930.2	0.0	4,805	0	15,161.0	0.0	NA	NA
VIN 1 or VaIN 1	4,744	0	14,936.6	0.0	4,805	0	15,161.0	0.0	NA	NA
VIN 2/3 or VaIN 2/3 or worse	4,744	0	14,936.6	0.0	4,805	0	15,161.0	0.0	NA	NA
HPV 11-Related Cervical, Vulvar, and Vaginal Disease	4,748	0	14,961.8	0.0	4,809	0	15,179.9	0.0	NA	NA
Cervical Disease	4,707	0	13,798.1	0.0	4,759	0	13,976.2	0.0	NA	NA
CIN 1	4,707	0	13,798.1	0.0	4,759	0	13,976.2	0.0	NA	NA
CIN 2 or worse	4,707	0	13,798.1	0.0	4,759	0	13,976.2	0.0	NA	NA
Vulvar and Vaginal Disease	4,744	0	14,936.6	0.0	4,805	0	15,161.0	0.0	NA	NA
Condyloma	4,744	0	14,936.6	0.0	4,805	0	15,161.0	0.0	NA	NA
VIN 1 or VaIN 1	4,744	0	14,936.6	0.0	4,805	0	15,161.0	0.0	NA	NA
VIN 2/3 or VaIN 2/3 or worse	4,744	0	14,936.6	0.0	4,805	0	15,161.0	0.0	NA	NA
HPV 16/18-Related Cervical, Vulvar, and Vaginal Disease	5,769	2	18,223.5	0.0	5,792	6	18,302.4	0.0	66.5	(-87.2, 95.1)
Cervical Disease	5,715	1	16,761.0	0.0	5,732	2	16,850.8	0.0	49.7	(-542.2, 98.3)
CIN 1	5,715	0	16,761.5	0.0	5,732	2	16,850.8	0.0	100	(-249.1, 100)
CIN 2 or worse	5,715	1	16,761.0	0.0	5,732	0	16,854.6	0.0	NA	NA
Vulvar and Vaginal Disease	5,762	1	18,192.3	0.0	5,789	4	18,284.6	0.0	74.9	(-92.9, 99.0)
Condyloma	5,762	1	18,192.3	0.0	5,789	1	18,288.0	0.0	-0.5	(≤ -999, 97.4)
VIN 1 or VaIN 1	5,762	0	18,195.6	0.0	5,789	2	18,287.9	0.0	100	(-249.0, 100)
VIN 2/3 or VaIN 2/3 or worse	5,762	0	18,195.6	0.0	5,789	2	18,287.0	0.0	100	(-249.0, 100)
HPV 16-Related Cervical, Vulvar, and Vaginal Disease	4,807	0	15,191.2	0.0	4,871	6	15,396.4	0.0	100	(31.9, 100)
Cervical Disease	4,782	0	14,112.6	0.0	4,844	2	14,311.8	0.0	100	(-252.1, 100)
CIN 1	4,782	0	14,112.6	0.0	4,844	2	14,311.8	0.0	100	(-252.1, 100)
CIN 2 or worse	4,782	0	14,112.6	0.0	4,844	0	14,315.6	0.0	NA	NA
Vulvar and Vaginal Disease	4,800	0	15,165.5	0.0	4,868	4	15,381.1	0.0	100	(-13.1, 100)
Condyloma	4,800	0	15,165.5	0.0	4,868	1	15,384.6	0.0	100	(≤ -999, 100)
VIN 1 or VaIN 1	4,800	0	15,165.5	0.0	4,868	2	15,384.5	0.0	100	(-252.2, 100)
VIN 2/3 or VaIN 2/3 or worse	4,800	0	15,165.5	0.0	4,868	2	15,383.6	0.0	100	(-252.2, 100)
HPV 18-Related Cervical, Vulvar, and Vaginal Disease	5,434	2	17,155.6	0.0	5,478	0	17,321.5	0.0	NA	NA
Cervical Disease	5,386	1	15,794.7	0.0	5,420	0	15,955.4	0.0	NA	NA
CIN 1	5,386	0	15,795.2	0.0	5,420	0	15,955.4	0.0	NA	NA
CIN 2 or worse	5,386	1	15,794.7	0.0	5,420	0	15,955.4	0.0	NA	NA
Vulvar and Vaginal Disease	5,429	1	17,125.8	0.0	5,475	0	17,300.6	0.0	NA	NA
Condyloma	5,429	1	17,125.8	0.0	5,475	0	17,300.6	0.0	NA	NA
VIN 1 or VaIN 1	5,429	0	17,129.1	0.0	5,475	0	17,300.6	0.0	NA	NA
VIN 2/3 or VaIN 2/3 or worse	5,429	0	17,129.1	0.0	5,475	0	17,300.6	0.0	NA	NA

† Percent reduction in the qHPV vaccine group incidence that was observed in the 9vHPV vaccine group, computed as 100x(1 - (9vHPV incidence/qHPV incidence)).

Subjects are counted once in each applicable endpoint category. A subject may appear in more than one category.

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.

n = Number of subjects who have at least one follow-up visit after Month 7.

9vHPV = Nine-Valent Human papillomavirus (Types 6, 11, 16, 18, 31, 33, 45, 52, 58) Recombinant Vaccine; qHPV = Quadrivalent Human papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine

CI = Confidence interval; CIN = Cervical intraepithelial neoplasia; HPV = Human papillomavirus; NA = Not available (i.e., not calculable); VaIN = Vaginal intraepithelial neoplasia; VIN = Vulvar intraepithelial neoplasia.

Table 21 presents the results of comparison of the 9vHPV vaccine group with the qHPV vaccine group with respect to cervical, vulvar, and vaginal disease related to HPV types 6, 11, 16, and 18 in the HNTS population.

Table 22. Impact of 9vHPV Vaccine on the Incidence of HPV 6/11/16/18-Related Cervical, Vulvar, and Vaginal Disease - median follow-up of 40 months post dose 3 (HPV-Naive Type-Specific Analysis Population)

	9vHPV Vaccine (N=7,099)				qHPV Vaccine (N=7,105)					
Endpoint	n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Risk Reduction† (%)	95% CI
HPV 6/11/16/18-Related Cervical, Vulvar, and Vaginal Disease	6,727	18	24,116.0	0.1	6,738	17	24,259.9	0.1	-6.5	(-109.2, 46.1)
Cervical Disease	6,592	5	22,384.4	0.0	6,599	9	22,500.7	0.0	44.2	(-70.4, 81.9)
CIN 1	6,592	4	22,384.9	0.0	6,599	5	22,504.9	0.0	19.6	(-199.4, 79.6)
CIN 2 or worse	6,592	1	22,394.2	0.0	6,599	5	22,508.0	0.0	79.9	(-49.6, 99.1)
Vulvar and Vaginal Disease	6,725	14	24,087.1	0.1	6,737	9	24,255.7	0.0	-56.6	(-307.6, 36.8)
Condyloma	6,725	11	24,091.5	0.0	6,737	5	24,259.9	0.0	-121.5	(-561.5, 24.2)
VIN 1 or VaIN 1	6,725	2	24,117.8	0.0	6,737	3	24,265.5	0.0	32.9	(-331.0, 91.7)
VIN 2/3 or VaIN 2/3 or worse	6,725	1	24,116.7	0.0	6,737	3	24,265.7	0.0	66.5	(-204.1, 98.7)
HPV 6/11-Related Cervical, Vulvar, and Vaginal Disease	5,462	14	19,574.4	0.1	5,510	7	19,862.1	0.0	-102.9	(-494.1, 17.3)
Cervical Disease	5,361	2	18,265.1	0.0	5,398	4	18,469.9	0.0	49.4	(-171.6, 93.2)
CIN 1	5,361	2	18,265.1	0.0	5,398	3	18,469.9	0.0	32.6	(-333.2, 91.6)
CIN 2 or worse	5,361	0	18,268.8	0.0	5,398	2	18,473.4	0.0	100	(-251.1, 100)
Vulvar and Vaginal Disease	5,460	13	19,548.5	0.1	5,509	4	19,849.8	0.0	-230.0	(-998.1, -6.2)
Condyloma	5,460	10	19,552.9	0.1	5,509	4	19,849.8	0.0	-153.8	(-774.2, 26.8)
VIN 1 or VaIN 1	5,460	2	19,576.0	0.0	5,509	1	19,855.6	0.0	-102.9	(≤ -999, 84.1)
VIN 2/3 or VaIN 2/3 or worse	5,460	1	19,574.9	0.0	5,509	0	19,857.4	0.0	NA	NA
HPV 6-Related Cervical, Vulvar, and Vaginal Disease	5,462	12	19,578.9	0.1	5,510	6	19,865.0	0.0	-102.9	(-447.5, 29.5)
Cervical Disease	5,361	2	18,265.1	0.0	5,398	4	18,469.9	0.0	49.4	(-171.6, 93.2)
CIN 1	5,361	2	18,265.1	0.0	5,398	3	18,469.9	0.0	32.6	(-333.2, 91.6)
CIN 2 or worse	5,361	0	18,268.8	0.0	5,398	2	18,473.4	0.0	100	(-251.1, 100)
Vulvar and Vaginal Disease	5,460	11	19,553.0	0.1	5,509	3	19,852.7	0.0	-272.3	(≤ -999, -1.5)
Condyloma	5,460	9	19,554.6	0.0	5,509	3	19,852.7	0.0	-204.6	(≤ -999, 16.9)
VIN 1 or VaIN 1	5,460	2	19,576.0	0.0	5,509	0	19,857.4	0.0	NA	NA
VIN 2/3 or VaIN 2/3 or worse	5,460	0	19,577.7	0.0	5,509	0	19,857.4	0.0	NA	NA
HPV 11-Related Cervical, Vulvar, and Vaginal Disease	5,462	2	19,602.2	0.0	5,510	1	19,876.0	0.0	-102.8	(≤ -999, 84.1)
Cervical Disease	5,361	0	18,268.8	0.0	5,398	0	18,473.4	0.0	NA	NA
CIN 1	5,361	0	18,268.8	0.0	5,398	0	18,473.4	0.0	NA	NA
CIN 2 or worse	5,361	0	18,268.8	0.0	5,398	0	18,473.4	0.0	NA	NA
Vulvar and Vaginal Disease	5,460	2	19,573.2	0.0	5,509	1	19,854.5	0.0	-102.9	(≤ -999, 84.1)
Condyloma	5,460	1	19,575.9	0.0	5,509	1	19,854.5	0.0	-1.4	(≤ -999, 97.4)
VIN 1 or VaIN 1	5,460	0	19,577.7	0.0	5,509	1	19,855.6	0.0	100	(≤ -999, 100)
VIN 2/3 or VaIN 2/3 or worse	5,460	1	19,574.9	0.0	5,509	0	19,857.4	0.0	NA	NA
HPV 16/18-Related Cervical, Vulvar, and Vaginal Disease	6,609	4	23,724.4	0.0	6,619	11	23,857.8	0.0	63.4	(-23.4, 89.2)
Cervical Disease	6,477	3	22,037.1	0.0	6,482	6	22,154.3	0.0	49.7	(-135.4, 89.1)
CIN 1	6,477	2	22,037.6	0.0	6,482	3	22,158.6	0.0	33.0	(-330.7, 91.7)
CIN 2 or worse	6,477	1	22,043.2	0.0	6,482	4	22,158.1	0.0	74.9	(-92.9, 99.0)
Vulvar and Vaginal Disease	6,607	1	23,693.3	0.0	6,618	6	23,845.3	0.0	83.2	(-25.1, 99.3)
Condyloma	6,607	1	23,693.3	0.0	6,618	2	23,849.5	0.0	49.7	(-543.0, 98.3)
VIN 1 or VaIN 1	6,607	0	23,696.5	0.0	6,618	2	23,850.0	0.0	100	(-249.5, 100)
VIN 2/3 or VaIN 2/3 or worse	6,607	0	23,696.5	0.0	6,618	3	23,848.3	0.0	100	(-72.5, 100)
HPV 16-Related Cervical, Vulvar, and Vaginal Disease	5,557	1	19,958.4	0.0	5,626	10	20,286.9	0.0	89.8	(34.9, 99.5)
Cervical Disease	5,447	1	18,695.1	0.0	5,510	5	19,014.7	0.0	79.7	(-51.4, 99.1)
CIN 1	5,447	1	18,695.1	0.0	5,510	3	19,015.2	0.0	66.1	(-207.4, 98.7)
CIN 2 or worse	5,447	0	18,697.8	0.0	5,510	3	19,018.5	0.0	100	(-74.4, 100)
Vulvar and Vaginal Disease	5,557	0	19,930.5	0.0	5,625	6	20,273.2	0.0	100	(31.7, 100)
Condyloma	5,557	0	19,930.5	0.0	5,625	2	20,277.4	0.0	100	(-253.3, 100)
VIN 1 or VaIN 1	5,557	0	19,930.5	0.0	5,625	2	20,277.9	0.0	100	(-253.3, 100)
VIN 2/3 or VaIN 2/3 or worse	5,557	0	19,930.5	0.0	5,625	3	20,276.2	0.0	100	(-74.4, 100)
HPV 18-Related Cervical, Vulvar, and Vaginal Disease	6,241	3	22,403.6	0.0	6,253	1	22,574.2	0.0	-202.3	(≤ -999, 66.7)
Cervical Disease	6,116	2	20,827.8	0.0	6,125	1	20,967.8	0.0	-101.3	(≤ -999, 84.2)
CIN 1	6,116	1	20,828.3	0.0	6,125	0	20,971.6	0.0	NA	NA
CIN 2 or worse	6,116	1	20,831.2	0.0	6,125	1	20,967.8	0.0	-0.7	(≤ -999, 97.4)
Vulvar and Vaginal Disease	6,239	1	22,370.8	0.0	6,252	0	22,553.9	0.0	NA	NA
Condyloma	6,239	1	22,370.8	0.0	6,252	0	22,553.9	0.0	NA	NA
VIN 1 or VaIN 1	6,239	0	22,374.0	0.0	6,252	0	22,553.9	0.0	NA	NA
VIN 2/3 or VaIN 2/3 or worse	6,239	0	22,374.0	0.0	6,252	0	22,553.9	0.0	NA	NA

† Percent reduction in the qHPV vaccine group incidence that was observed in the 9vHPV vaccine group, computed as 100x(1 - (9vHPV incidence/qHPV incidence)).

Subjects are counted once in each applicable endpoint category. A subject may appear in more than one category.

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.

n = Number of subjects who have at least one follow-up visit after Day 1.

9vHPV = Nine-Valent Human papillomavirus (Types 6, 11, 16, 18, 31, 33, 45, 52, 58) Recombinant Vaccine; qHPV = Quadrivalent Human papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine

CI = Confidence interval; CIN = Cervical intraepithelial neoplasia; HPV = Human papillomavirus; NA = Not available (i.e., not calculable); VaIN = Vaginal intraepithelial neoplasia; VIN = Vulvar intraepithelial neoplasia.

Table 22 presents the results of comparisons of the 9vHPV and the qHPV vaccine groups with respect to the incidence of persistent infection related to HPV types 6, 11, 16, and 18 in the PPE and HNTS populations.

Table 23. Impact of 9vHPV Vaccine on the Incidence of HPV 6/11/16/18-Related Persistent Infection - median follow-up of 40 months post dose 3 (PPE and HN-TS Analysis Populations)

	9vHPV Vaccine (N=7,099)				qHPV Vaccine (N=7,105)					
Analysis Population Endpoint	n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Risk Reduction† (%)	95% CI
Per-Protocol Efficacy (PPE)										
Persistent Infection ≥6 Months‡										
HPV 6/11/16/18-Related	5,812	59	16,187.1	0.4	5,830	80	16,151.4	0.5	26.4	(-4.3, 47.5)
HPV 6/11-Related	4,697	13	13,160.0	0.1	4,757	7	13,278.5	0.1	-87.4	(-454.7, 29.5)
HPV 6-Related	4,697	13	13,159.7	0.1	4,757	7	13,278.5	0.1	-87.4	(-454.7, 29.5)
HPV 11-Related	4,697	0	13,174.9	0.0	4,755	0	13,280.5	0.0	NA	NA
HPV 16/18-Related	5,704	46	15,917.1	0.3	5,729	73	15,893.8	0.5	37.1	(8.8, 57.5)
HPV 16-Related	4,772	37	13,404.7	0.3	4,841	64	13,488.9	0.5	41.8	(13.6, 62.3)
HPV 18-Related	5,374	9	15,049.6	0.1	5,416	9	15,145.8	0.1	-0.6	(-186.2, 64.6)
Persistent Infection ≥12 Months‡										
HPV 6/11/16/18-Related	5,812	22	16,239.4	0.1	5,830	32	16,219.6	0.2	31.3	(-21.9, 60.4)
HPV 6/11-Related	4,697	7	13,166.2	0.1	4,757	1	13,284.4	0.0	-606.3	(≤ -999, -0.9)
HPV 6-Related	4,697	7	13,165.3	0.1	4,757	1	13,284.4	0.0	-606.3	(≤ -999, -0.9)
HPV 11-Related	4,697	0	13,174.9	0.0	4,755	0	13,280.5	0.0	NA	NA
HPV 16/18-Related	5,704	15	15,962.8	0.1	5,729	31	15,956.0	0.2	51.6	(9.4, 75.7)
HPV 16-Related	4,772	9	13,447.3	0.1	4,841	24	13,549.7	0.2	62.2	(17.1, 82.6)
HPV 18-Related	5,374	6	15,052.6	0.0	5,416	7	15,147.2	0.0	13.7	(-185.8, 71.0)
HPV-Naïve Type-Specific (HN-TS)										
Persistent Infection ≥6 Months‡										
HPV 6/11/16/18-Related	6,562	147	21,219.7	0.7	6,582	180	21,218.1	0.8	18.3	(-2.1, 34.8)
HPV 6/11-Related	5,340	47	17,469.2	0.3	5,385	32	17,640.5	0.2	-48.3	(-133.6, 7.3)
HPV 6-Related	5,340	43	17,479.4	0.2	5,385	29	17,647.3	0.2	-49.7	(-148.6, 8.7)
HPV 11-Related	5,340	4	17,561.9	0.0	5,385	3	17,701.2	0.0	-34.4	(-582.0, 70.7)
HPV 16/18-Related	6,448	106	20,972.3	0.5	6,465	149	20,946.2	0.7	28.9	(8.6, 44.7)
HPV 16-Related	5,425	82	17,800.1	0.5	5,495	118	18,005.3	0.7	29.7	(7.3, 47.6)
HPV 18-Related	6,088	26	19,968.2	0.1	6,109	32	20,030.4	0.2	18.5	(-40.6, 51.7)
Persistent Infection ≥12 Months‡										
HPV 6/11/16/18-Related	6,562	92	21,313.8	0.4	6,582	102	21,357.6	0.5	9.6	(-21.0, 32.6)
HPV 6/11-Related	5,340	32	17,498.6	0.2	5,385	20	17,659.8	0.1	-61.5	(-197.9, 10.4)
HPV 6-Related	5,340	28	17,508.2	0.2	5,385	18	17,665.1	0.1	-56.9	(-201.3, 16.2)
HPV 11-Related	5,340	4	17,561.9	0.0	5,385	2	17,701.9	0.0	-101.6	(≤ -999, 62.5)
HPV 16/18-Related	6,448	62	21,049.0	0.3	6,465	83	21,066.5	0.4	25.2	(-5.1, 47.1)
HPV 16-Related	5,425	44	17,868.0	0.2	5,495	60	18,108.9	0.3	25.7	(-9.7, 50.5)
HPV 18-Related	6,088	19	19,979.9	0.1	6,109	23	20,047.3	0.1	17.1	(-59.1, 57.0)

† Percent reduction in the qHPV vaccine group incidence that was observed in the 9vHPV vaccine group, computed as 100x(1 - (9vHPV incidence/qHPV incidence)).

‡ ±1 month visit window.

Subjects are counted once in each applicable endpoint category. A subject may appear in more than one category.

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.

n = Number of subjects in the given population who have at least one follow-up visit after Month 7 in the per-protocol population; after Day 1 in all other analysis populations.

9vHPV = Nine-Valent Human papillomavirus (Types 6, 11, 16, 18, 31, 33, 45, 52, 58) Recombinant Vaccine; qHPV = Quadrivalent Human papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine.

CI = Confidence interval; HPV = Human papillomavirus; NA = Not available (i.e., not calculable).

The results for Pap abnormalities and Cervical and External Genital Procedures and Cervical Definitive Therapy related to HPV 1/11/16/18 were in agreement with the primary and other secondary and exploratory endpoints, i.e. there were only small differences between the groups, with slightly lower incidences of disease endpoints related to HPV 16 in the 9vHPV group compared to the qHPV group and higher incidence of HPV 6 related outcomes in the9vHPV group compared to the qHPV group.

In summary, the number of cases of the clinical endpoints related to HPV6/11/16/18 in the PP population was low, as expected. Of the 6 cases in the 9vHPV group 4 were condyloma related to HPV6. In the qHPV group 6 of the 7 cases were related to HPV16, and they were also co-infected with non-vaccine high-risk HPV types on or before the time of becoming a case of HPV16-related disease. The number of cases in the HNST population was higher, but the results were consistent with the PP population results. The results for persistent infections are also in agreement with the results for the primary endpoints, i.e. there are only small differences between the groups and the 9vHPV group had higher incidences of persistent infections with HPV 6/11 compared to the qHPV group, and lower incidence of persistent infection with HPV 16/18 compared to the qHPV group.

Efficacy of 9vHPV compared to historical placebo

These supportive analyses consist in the assessment of 9vHPV vaccine efficacy relative to historic placebo (i.e. placebo arm of the qHPV vaccine clinical program) to prevent HPV 6-, HPV 11-, HPV 16-, and HPV 18-related persistent infection and cervical, vulvar, and vaginal disease. They intend to demonstrate that placebo-normalized efficacy of 9vHPV vaccine is non-inferior to placebo-normalized efficacy of qHPV vaccine to prevent HPV 16- and HPV 18-related persistent infection and disease, which would show high efficacy of the 9vHPV vaccine and no negative trend in efficacy compared with qHPV vaccine.

Results presented in this section represent the efficacy of the 9vHPV vaccine in preventing HPV 6/11/16/18-related persistent infection and disease relative to an unvaccinated (with HPV vaccine) population (i.e. compared to a historical placebo group).

Table 23 shows the results of evaluation of the efficacy of the 9vHPV vaccine relative to historical placebo with respect to persistent infection, cervical, vulvar, and vaginal disease related to HPV types 16 and 18 for each of the PPE and HNTS populations.

Table 24. Analysis of Efficacy Against HPV 16/18-Related Persistent Infection ⩾6 Months (±1 Month Visit Window), Cervical, Vulvar, and Vaginal Disease 9vHPV Vaccine versus Historical Placebo (PPE and HN-TS Analysis Populations)

	Current Study				Historical Cohorts[†]					
	9vHPV Vaccine (N=7,099)		qHPV Vaccine (N=7,105)		qHPV Vaccine (N=9,075)		Placebo (N=9,075)		9vHPV Vaccine vs. Placebo	
Analysis Population Endpoint	No. of Cases/n	Incidence Rate per 100 Person-Years At Risk	No. of Cases/n	Incidence Rate per 100 Person-Years At Risk	No. of Cases/n	Incidence Rate per 100 Person-Years At Risk	No. of Cases/n	Incidence Rate per 100 Person-Years At Risk	Vaccine Efficacy[‡] (%)	(95% CI)[‡]
Per-Protocol Efficacy (PPE)										
Persistent Infection, Cervical, Vulvar, and Vaginal Disease[§]	47 / 5,769	0.3	75 / 5,792	0.4	3 / 1,679	0.1	206 / 1,693	4.2	99.0	(96.9, 99.7)
Persistent Infection ⩾ 6 Months Duration	46 / 5,704	0.3	73 / 5,729	0.5	3 / 1,669	0.1	203 / 1,681	4.3	99.0	(96.8, 99.7)
Cervical, Vulvar, and Vaginal Disease	2 / 5,769	0.0	6 / 5,792	0.0	9 / 7,775	0.0	223 / 7,744	1.0	98.4	(92.0, 99.7)
Cervical Disease	1 / 5,715	0.0	2 / 5,732	0.0	9 / 7,738	0.0	181 / 7,714	0.8	96.9	(73.8, 99.6)
CIN 1	0 / 5,715	0.0	2 / 5,732	0.0	7 / 7,738	0.0	133 / 7,714	0.6	98.9	(74.5, 100)
CIN 2 or worse	1 / 5,715	0.0	0 / 5,732	0.0	2 / 7,738	0.0	100 / 7,714	0.4	92.6	(-131.7, 99.8)
Vulvar and Vaginal Disease	1 / 5,762	0.0	4 / 5,789	0.0	0 / 7,772	0.0	57 / 7,744	0.2	99.7	(91.8, 100)
Condyloma	1 / 5,762	0.0	1 / 5,789	0.0	0 / 7,772	0.0	34 / 7,744	0.1	98.5	(47.2, 100)
VIN 1 or VaIN 1	0 / 5,762	0.0	2 / 5,789	0.0	0 / 7,772	0.0	9 / 7,744	0.0	98.9	(32.4, 100)
VIN 2/3 or VaIN 2/3 or worse	0 / 5.762	0.0	2 / 5.789	0.0	0 / 7.772	0.0	19 / 7.744	0.1	99.5	(67.9. 100)
HPV-Naive Type-Specific (HN-TS)										
Persistent Infection, Cervical, Vulvar, and Vaginal Disease[§]	108 / 6,609	0.5	151 / 6,619	0.6	20 / 1,969	0.3	287 / 1,964	4.6	95.3	(92.1, 97.2)
Persistent Infection ⩾ 6 Months Duration	106 / 6,448	0.5	149 / 6,465	0.7	20 / 1,937	0.3	284 / 1,931	4.7	95.2	(92.0, 97.1)
Cervical, Vulvar, and Vaginal Disease	4 / 6,609	0.0	11 / 6,619	0.0	16 / 8,648	0.1	322 / 8,680	1.1	98.0	(93.4, 99.4)
Cervical Disease	3 / 6,477	0.0	6 / 6,482	0.0	14 / 8,512	0.0	257 / 8,564	0.9	97.0	(87.6, 99.3)
CIN 1	2 / 6,477	0.0	3 / 6,482	0.0	10 / 8,512	0.0	192 / 8,564	0.7	96.1	(77.7, 99.3)
CIN 2 or worse	1 / 6,477	0.0	4 / 6,482	0.0	4 / 8,512	0.0	139 / 8,564	0.5	98.9	(91.4, 99.9)
Vulvar and Vaginal Disease	1 / 6,607	0.0	6 / 6,618	0.0	2 / 8,642	0.0	87 / 8,673	0.3	99.3	(94.1, 99.9)
Condyloma	1 / 6,607	0.0	2 / 6,618	0.0	1 / 8,642	0.0	45 / 8,673	0.2	98.0	(73.2, 99.9)
VIN 1 or VaIN 1	0 / 6,607	0.0	2 / 6,618	0.0	0 / 8,642	0.0	17 / 8,673	0.1	99.4	(63.8, 100)
VIN 2/3 or VaIN 2/3 or worse	0 / 6,607	0.0	3 / 6,618	0.0	1 / 8,642	0.0	34 / 8,673	0.1	99.4	(81.5, 100)

[†] Historical cohorts included qHPV vaccine and placebo groups from V501 protocols 007, 011, 012, and 015. Data on HPV 16/18-related persistent infection are available only from protocols 007 and 012.

[‡] Vaccine efficacy and its associated 95% confidence interval were computed using the indirect method proposed by Hasselblad and Kong.

[§]Historical cohorts included qHPV vaccine and placebo groups from V501 protocols 007 and 012 only.

Subjects are counted once in each applicable endpoint category. A subject may appear in more than one category.

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.

n = Number of subjects in the given population who have at least one follow-up visit after Month 7 in the per-protocol population; after Day 1 in all other analysis populations.

9vHPV = Nine-Valent Human papillomavirus (Types 6, 11, 16, 18, 31, 33, 45, 52, 58) Recombinant Vaccine; qHPV = Quadrivalent Human papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine

CI = Confidence interval; CIN = Cervical intraepithelial neoplasia; HPV = Human papillomavirus; VaIN = Vaginal intraepithelial neoplasia; VIN = Vulvar intraepithelial neoplasia

Table 24 shows the results of evaluation of the efficacy of the 9vHPV vaccine relative to historical placebo with respect to persistent infection, cervical, vulvar, and vaginal disease related to HPV types 6 and 11 for each of the PPE and HNTS populations.

Table 25. Analysis of Efficacy Against HPV 6/11-Related Persistent Infection ⩾6 Months (±1 Month Visit Window), Cervical, Vulvar, and Vaginal Disease 9vHPV Vaccine versus Historical Placebo (PPE and HN-TS Analysis Populations)

	Current Study				Historical Cohorts †					
	9vHPV Vaccine (N=7,099)		qHPV Vaccine (N=7,105)		qHPV Vaccine (N=9,075)		Placebo (N=9,075)		9vHPV Vaccine vs. Placebo	
Analysis Population Endpoint	No. of Cases/n	Incidence Rate per 100 Person-Years At Risk	No. of Cases/n	Incidence Rate per 100 Person-Years At Risk	No. of Cases/n	Incidence Rate per 100 Person-Years At Risk	No. of Cases/n	Incidence Rate per 100 Person-Years At Risk	Vaccine Efficacy‡ (%)	(95% CI)‡
Per-Protocol Efficacy (PPE)										
Persistent Infection ≥ 6 Months Duration	13 / 4,697	0.1	7 / 4,757	0.1	0 / 214	0.0	11 / 209	1.6	92.0	(-54.9, 99.6)
Cervical, Vulvar, and Vaginal Disease	4 / 4,748	0.0	1 / 4,809	0.0	2 / 6,935	0.0	241 / 6,856	1.2	96.9	(71.3, 99.7)
Cervical Disease	0 / 4,707	0.0	1 / 4,759	0.0	0 / 6,902	0.0	57 / 6,828	0.3	99.7	(79.9, 100)
CIN 1	0 / 4,707	0.0	0 / 4,759	0.0	0 / 6,902	0.0	45 / 6,828	0.2	98.9	(-34.4, 100)
CIN 2 or worse	0 / 4,707	0.0	1 / 4,759	0.0	0 / 6,902	0.0	16 / 6,828	0.1	99.0	(28.5, 100)
Vulvar and Vaginal Disease	4 / 4,744	0.0	0 / 4,805	0.0	2 / 6,932	0.0	205 / 6,856	1.0	89.1	(-161.2, 99.5)
Condyloma	4 / 4,744	0.0	0 / 4,805	0.0	2 / 6,932	0.0	189 / 6,856	0.9	88.2	(-183.6, 99.5)
VIN 1 or VaIN 1	0 / 4,744	0.0	0 / 4,805	0.0	0 / 6,932	0.0	22 / 6,856	0.1	97.8	(-176.4, 100)
VIN 2/3 or VaIN 2/3 or worse	0 / 4,744	0.0	0 / 4,805	0.0	0 / 6,932	0.0	7 / 6,856	0.0	93.3	(-759.8, 99.9)
HPV-Naive Type-Specific (HN-TS)										
Persistent Infection ≥ 6 Months Duration	47 / 5,340	0.3	32 / 5,385	0.2	0 / 233	0.0	17 / 234	2.0	95.8	(27.8, 99.8)
Cervical, Vulvar, and Vaginal Disease	14 / 5,462	0.1	7 / 5,510	0.0	11 / 7,776	0.0	314 / 7,799	1.2	92.9	(79.4, 97.5)
Cervical Disease	2 / 5,361	0.0	4 / 5,398	0.0	2 / 7,652	0.0	75 / 7,697	0.3	98.1	(86.3, 99.7)
CIN 1	2 / 5,361	0.0	3 / 5,398	0.0	2 / 7,652	0.0	61 / 7,697	0.2	97.1	(77.0, 99.6)
CIN 2 or worse	0 / 5,361	0.0	2 / 5,398	0.0	0 / 7,652	0.0	20 / 7,697	0.1	99.5	(69.2, 100)
Vulvar and Vaginal Disease	13 / 5,460	0.1	4 / 5,509	0.0	9 / 7,769	0.0	265 / 7,792	1.0	89.2	(62.3, 96.9)
Condyloma	10 / 5,460	0.1	4 / 5,509	0.0	9 / 7,769	0.0	246 / 7,792	0.9	90.9	(67.3, 97.5)
VIN 1 or VaIN 1	2 / 5,460	0.0	1 / 5,509	0.0	2 / 7,769	0.0	25 / 7,792	0.1	83.3	(-84.6, 98.5)
VIN 2/3 or VaIN 2/3 or worse	1 / 5,460	0.0	0 / 5,509	0.0	0 / 7,769	0.0	9 / 7,792	0.0	83.9	(≤ -999, 99.8)

† Historical cohorts included qHPV vaccine and placebo groups from V501 protocols 007, 011, 012, and 015. Data on HPV 6/11-related persistent infection are available only from protocol 007.
‡ Vaccine efficacy and its associated 95% confidence interval were computed using the indirect method proposed by Hasselblad and Kong.
Subjects are counted once in each applicable endpoint category. A subject may appear in more than one category.
N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects in the given population who have at least one follow-up visit after Month 7 in the per-protocol population; after Day 1 in all other analysis populations.
9vHPV = Nine-Valent Human papillomavirus (Types 6, 11, 16, 18, 31, 33, 45, 52, 58) Recombinant Vaccine; qHPV = Quadrivalent Human papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine
CI = Confidence interval; CIN = Cervical intraepithelial neoplasia; HPV = Human papillomavirus; VaIN = Vaginal intraepithelial neoplasia; VIN = Vulvar intraepithelial neoplasia

The confidence intervals are very wide for most endpoints, although the point estimates do not indicate a negative trend in protection against any endpoint.

Results presented in Table 25 addresses the exploratory efficacy objective #2. The analysis is a comparison of the efficacy of each of the 9vHPV and qHPV vaccines relative to a historical placebo (i.e., efficacy is the percent reduction in the historical placebo group incidence that is observed in each vaccination group). The pre-specified success criterion is the lower bound of the 95% confidence interval for the difference of efficacy (9vHPV – qHPV) should be greater than −15 percentage points. As shown in Table 24, the lower bound of the 95% CI for the difference of efficacy between the 9vHPV and qHPV vaccines is 0.8%, which is greater than −15%, thus demonstrating the non-inferiority of the 9vHPV vaccine compared to the qHPV vaccine in preventing persistent infection, cervical, vulvar, and vaginal disease related to HPV types 16 and 18.

Table 26. Non-Inferiority Analysis: Comparison of 9vHPV versus qHPV Vaccine Efficacy Against HPV 16/18-Related Persistent Infection > 6 Months (+1 Month Visit Window), Cervical, Vulvar, and Vaginal Disease - median follow-up of 40 months post dose 3 (Per-Protocol Efficacy Population)

	9vHPV Vaccine (N=7,099)		qHPV Vaccine (N=7,105)		Difference in RRh (95% CI) (9vHPV – qHPV)
Endpoint	Cases (Incidence†)	RRh‡ (95% CI)	Cases (Incidence†)	RRh§ (95% CI)	
HPV 16/18-Related Persistent Infection, Cervical, Vulvar, and Vaginal Disease	47 (0.26)	93.5% (91.5%, 95.3%)	75 (0.41)	89.8% (87.0%, 92.0%)	3.8% (0.8%, 7.2%)

† Rate per 100 person-years at risk.
‡ Percent reduction in the historical placebo group incidence that was observed in the 9vHPV vaccine group, computed as 100x{1 – (9vHPV incidence/4.0)}.
§ Percent reduction in the historical placebo group incidence that was observed in the qHPV vaccine group, computed as 100x{1 – (qHPV incidence/4.0)}.
N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
9vHPV = Nine-Valent Human papillomavirus (Types 6, 11, 16, 18, 31, 33, 45, 52, 58) Recombinant Vaccine; qHPV = Quadrivalent Human papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine.
HPV = Human papillomavirus; RRh = Risk reduction relative to historical placebo (in percent).

The comparison of the efficacy results of 9vHPV and historical placebo controls are of interest, although there are limitations of this type of comparison as other biases may interfere. The incidence of disease outcomes

related to HPV 16/18 in the qHPV group was for instance higher in the current study compared to the historical qHPV group as seen in table 23 above. However, non-inferiority of the 9HPV compared to qHPV in table 25 was clearly demonstrated, although the absolute risk reductions should be interpreted with caution.

Additional efficacy analysis related to all 9 vaccine HPV types (end of study results)

Further exploratory analyses were conducted in PPE population to evaluate vaccine efficacy against disease and invasive procedures causally related to all 9 vaccine HPV types: relative to the qHPV vaccine, the 9vHPV vaccine demonstrated efficacy of:

- 94.4% (95% CI 78.8 ; 99.0) against CIN2 and worse (with 2/5,952 versus 36/5,947 cases - 9vHPV vs. qHPV respectively), and 100% (95% CI 46.3 ; 100.0) against CIN3 (with 0/5,952 versus 8/5,947 cases respectively).
- 95.9% (95% CI 92.7 ; 97.9) against cervical biopsy (with 11/6016 versus 262/6018 cases respectively) and 90.7% (95% CI 76.3 ; 97.0) against cervical definitive therapy (with 4/6016 versus 43/6018 cases respectively).

HPV 35/39/51/56/59-Related Endpoints

Neither the 9vHPV vaccine nor the qHPV vaccine contains virus-like particles of HPV types 35, 39, 51, 56, and 59. As such, neither vaccine is expected to confer prophylactic efficacy against persistent infection and disease endpoints related to these 5 HPV types. Similar to the above section the comparison of the 9vHPV vaccine group with the qHPV vaccine group with respect to HPV 35/39/51/56/59-related endpoints is an assessment of similarity of the incidences of these endpoints in the two vaccine groups. In summary:

- For each of HPV types 35, 39, 51, 56, and 59, the incidences of HPV type-related persistent infection, cervical, vulvar, and vaginal disease endpoints were similar in each of the two vaccine groups.

The cumulative incidence distribution of the composite endpoint of persistent infection, cervical, vulvar, and vaginal disease related to any of HPV types 35, 39, 51, 56, and 59 in the All-HN population is shown in Figure 3. The 9vHPV and qHPV vaccine groups have similar cumulative incidence distribution with respect to this composite endpoint. As expected there were no relevant differences between 9HPV and qHPV in incidence of HPV35/39/51/56/59-related endpoints.

Therapeutic efficacy against HPV vaccine types

The qHPV vaccine has not been shown to confer a therapeutic efficacy benefit. It is not expected that the 9vHPV vaccine will confer a therapeutic efficacy benefit. The data are not presented in detail but in summary:

- There is no consistent efficacy trend suggesting that the 9vHPV vaccine is efficacious in reducing the incidences of HPV 31/33/45/52/58-related persistent infection and disease endpoints in S1P0, S0P1, and S1P1 populations.
- There is no consistent efficacy trend suggesting that the 9vHPV vaccine is efficacious in preventing HPV 6/11/16/18-related persistent infection and disease endpoints in S1P0, S0P1, and S1P1 populations.
- In each of S1P0, S0P1, and S1P1 analysis populations, the incidences of HPV 6/11/16/18-related persistent infection, cervical, vulvar, and vaginal disease in a 9vHPV vaccinated population are at least comparable and no worse than the corresponding incidences in a qHPV vaccinated population.

Immunogenicity results

Dose-Ranging Substudy

The primary immunogenicity objective for the dose-ranging substudy was to evaluate the selected dose of 9vHPV vaccine for use in efficacy evaluation. Table 26 presents a per-protocol summary of observed anti-HPV 6, anti-HPV 11, anti-HPV 16, anti-HPV 18, anti-HPV 31, anti-HPV 33, anti-HPV 45, anti-HPV 52, and anti-HPV 58 GMTs at Day 1, Month 3, and Month 7, with associated 95% CI's, by vaccination group. The table shows that GMTs for HPV Types 6, 11, 16 and 18 increased substantially following the 2nd and 3rd vaccine administrations in both the qHPV vaccine and the 9vHPV vaccine groups. Likewise, GMTs for HPV Types 31, 33, 45, 52, and 58 increased substantially following each vaccine administration in the 9vHPV vaccine groups. Marked immune responses were generally observed as early as Month 3. The highest GMTs for all HPV types were observed at Month 7 in all vaccine groups.

Table 27. Summary of Anti-HPV cLIA Geometric Mean Titres by Vaccination Group (Per-Protocol Immunogenicity Population - Dose-Ranging Substudy)

Assay (cLIA)	Low-Dose 9vHPV Vaccine (N=312)			Mid-Dose 9vHPV Vaccine (N=307)			High-Dose 9vHPV Vaccine (N=310)			qHPV Vaccine (N=310)		
Time Point	n	GMT (mMU/mL)	95% CI	n	GMT (mMU/mL)	95% CI	n	GMT (mMU/mL)	95% CI	n	GMT (mMU/mL)	95% CI
Anti-HPV 6												
Day 1	200	< 10	(<10, <10)	186	< 16	(<16, <16)	207	< 10	(<10, <10)	196	< 16	(<16, <16)
Month 03	198	480.7	(422.9, 546.5)	184	550.2	(481.7, 628.4)	204	574.1	(506.0, 651.4)	192	553.3	(485.8, 630.2)
Month 07	200	598.3	(524.2, 682.8)	186	673.1	(586.9, 771.9)	207	689.0	(605.1, 784.6)	196	542.1	(474.4, 619.5)
Anti-HPV 11												
Day 1	200	< 7	(<7, <7)	186	< 6	(<6, <6)	207	< 7	(<7, <7)	196	< 6	(<6, <6)
Month 03	198	508.9	(450.1, 575.3)	184	543.7	(478.7, 617.4)	204	504.5	(447.1, 569.3)	192	631.7	(557.7, 715.5)
Month 07	200	571.3	(509.5, 640.5)	186	549.6	(488.1, 618.8)	207	564.7	(504.7, 632.0)	196	660.6	(588.5, 741.6)
Anti-HPV 16												
Day 1	198	< 9	(<9, <9)	205	< 12	(<12, <12)	194	< 9	(<9, <9)	201	< 12	(<12, <12)
Month 03	196	1,350.0	(1,154.3, 1,579.0)	201	1,432.7	(1,227.3, 1,672.4)	191	1,602.7	(1,367.5, 1,878.3)	197	1,524.0	(1,303.5, 1,781.8)
Month 07	198	1,874.6	(1,626.3, 2,160.8)	205	2,310.9	(2,009.7, 2,657.2)	194	2,422.4	(2,098.5, 2,796.4)	201	1,847.9	(1,604.8, 2,127.8)
Anti-HPV 18												
Day 1	218	< 15	(<15, <15)	229	< 8	(<8, <8)	233	< 15	(<15, <15)	223	< 8	(<8, <8)
Month 03	215	322.1	(276.8, 374.7)	225	422.4	(364.3, 489.7)	231	448.4	(387.5, 518.9)	219	353.6	(304.3, 410.8)
Month 07	218	603.8	(525.3, 694.1)	229	785.2	(685.4, 899.6)	233	788.8	(689.4, 902.6)	223	635.5	(553.7, 729.3)
Anti-HPV 31												
Day 1	212	< 6	(<6, <6)	217	< 4	(<4, <4)	221	< 6	(<6, <6)	212	< 4	(<4, <4)
Month 03	209	311.8	(261.0, 372.5)	212	323.5	(271.2, 386.0)	218	337.4	(283.5, 401.6)	208	8.0	(6.7, 9.5)
Month 07	212	585.7	(511.4, 670.8)	217	545.0	(476.7, 623.2)	221	599.4	(524.8, 684.5)	212	8.0	(7.0, 9.2)
Anti-HPV 33												
Day 1	230	< 4	(<4, <4)	239	< 4	(<4, <4)	230	< 4	(<4, <4)	224	< 4	(<4, <4)
Month 03	227	175.8	(149.8, 206.2)	234	164.8	(140.8, 192.9)	228	177.5	(151.3, 208.2)	220	< 4	(<4, 4.3)
Month 07	230	293.9	(262.6, 328.8)	239	296.0	(265.1, 330.5)	230	330.0	(294.9, 369.3)	224	< 4	(<4, 4.0)
Anti-HPV 45												
Day 1	229	< 4	(<4, <4)	239	< 3	(<3, <3)	237	< 4	(<4, <4)	225	< 3	(<3, <3)
Month 03	226	109.3	(92.0, 129.9)	235	112.7	(95.1, 133.4)	234	116.3	(98.2, 137.8)	221	< 4	(<4, <4)
Month 07	229	235.5	(207.2, 267.6)	239	225.9	(199.3, 256.1)	237	250.2	(220.6, 283.7)	225	< 4	(<4, <4)
Anti-HPV 52												
Day 1	200	< 2	(<2, <2)	215	< 3	(<3, <3)	213	< 2	(<2, <2)	212	< 3	(<3, <3)
Month 03	198	192.6	(161.0, 230.5)	211	201.5	(169.3, 239.8)	211	219.2	(184.1, 260.8)	208	< 2	(<2, 2.1)
Month 07	200	319.6	(279.8, 365.1)	215	351.2	(308.9, 399.2)	213	406.7	(357.6, 462.6)	212	< 2	(<2, <2)
Anti-HPV 58												
Day 1	222	< 3	(<3, <3)	231	< 4	(<4, <4)	223	< 3	(<3, <3)	210	< 4	(<4, <4)
Month 03	219	206.4	(173.9, 244.9)	226	194.6	(164.4, 230.3)	221	234.7	(198.0, 278.4)	206	4.0	(3.4, 4.8)
Month 07	222	369.5	(326.5, 418.0)	231	371.5	(329.1, 419.3)	223	444.1	(392.6, 502.3)	210	< 3	(<3, 3.1)

The per-protocol immunogenicity population includes all subjects who were not general protocol violators, received all 3 vaccinations within acceptable day ranges, were seronegative at Day 1 and PCR negative Day 1 through Month 7 for the relevant HPV type(s), and had a Month 7 serum sample collected within an acceptable day range.

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.

n = Number of subjects contributing to the analysis.

CI = Confidence interval; cLIA = Competitive Luminex immunoassay; GMT = Geometric mean titer; mMU = Milli Merck units.

Seropositivity: Vaccinated subjects were considered seropositive for a given HPV type if their HPV-9 cLIA titre for this HPV type was greater than the serostatus cut-off. At Day 1, all subjects were seronegative to all HPV types tested. Seroconversion rates for HPV Types 6, 11, 16, and 18 increased substantially following the 2nd vaccine injection in both the qHPV vaccine and the 9vHPV vaccine groups. Likewise, seroconversion rates for HPV Types 31, 33, 45, 52, and 58 increased substantially following the 2nd vaccine injection in the 9vHPV vaccine groups. At Month 7, more than 99% of subjects had seroconverted for HPV Types 6, 11, 16 and 18 in both the qHPV vaccine group and the 9vHPV vaccine groups, and over 98% of subjects had seroconverted for HPV Types 31, 33, 45, 52, and 58 in the 9vHPV vaccine groups.

In summary, the differences in GMTs between the three dose levels of 9vHPV were small for all HPV types. The selected dose was the mid-dose, which was compared to the qHPV in a non-inferiority analysis as shown below.

In order to address the primary immunogenicity objective of dose-ranging study, GMTs at 4 weeks Post-dose 3 were compared between the qHPV vaccine group and the selected 9vHPV vaccine group for use in efficacy analyses. A statistical analysis was conducted (at a multiplicity-adjusted [due to the dose-selection interim analysis] 1-sided α=0.0247 level) to assess whether or not anti-HPV 6, 11, 16 and 18 cLIA GMTs at 4 weeks Post-dose 3 in subjects vaccinated with selected 9vHPV vaccine were non-inferior to anti-HPV 6, 11, 16 and 18 cLIA GMTs at 4 weeks Post-dose 3 in subjects vaccinated with qHPV vaccine. Table 27 presents the results of the per-protocol analysis of non-inferiority comparing Month 7 cLIA GMTs between subjects who received the selected 9vHPV vaccine and subjects who received qHPV vaccine. The statistical criterion for non-inferiority with respect to GMT required that the lower bound of the 95.06% CI for the fold-difference in anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 GMTs (selected 9vHPV vaccine/qHPV vaccine) was above 0.5, to exclude a decrease of 2-fold or more. The table shows that the non-inferiority hypothesis of GMT responses for each of the HPV Types 6, 11, 16, and 18 in the selected 9vHPV vaccine relative to GMT responses in the qHPV vaccine group at 4 weeks Post-dose 3 was met in the PPI population with p-values < 0.001. The confidence intervals for HPV types 6, 16 and 18 were above 1 and for HPV type 11 the confidence interval were below 1.

Table 28. Statistical Analysis of Non-Inferiority Comparing Month 7 HPV cLIA Geometric Mean Titres (HPV-types 6, 11, 16 and 18) Between Subjects Who Received the Selected Dose Formulation of 9vHPV Vaccine and Subjects Who Received qHPV Vaccine (Per-Protocol Immunogenicity Population - Dose-Ranging Substudy)

	Comparison Group					
	9vHPV Vaccine (Comparison Group A) (N = 307)		qHPV Vaccine (Comparison Group B) (N = 310)		Estimated Fold Difference Group A / Group B	p-Value for
Assay (cLIA)	n	Estimated GMT (mMU/mL)	n	Estimated GMT (mMU/mL)	(95.06% CI)	Non-Inferiority‡
Anti-HPV 6	186	673.1	196	542.1	1.24 (1.03, 1.50)	<0.001
Anti-HPV 11	186	549.6	196	660.6	0.83 (0.71, 0.98)	<0.001
Anti-HPV 16	205	2,310.9	201	1,847.9	1.25 (1.02, 1.53)	<0.001
Anti-HPV 18	229	785.2	223	635.5	1.24 (1.02, 1.50)	<0.001
Overall conclusion: The non-inferiority criteria was met for all 4 HPV types.						

†The per-protocol immunogenicity population includes all subjects who were not general protocol violators, received all 3 vaccinations within acceptable day ranges, were seronegative at Day 1 and PCR negative Day 1 through Month 7 for the relevant HPV type(s), and had a Month 7 serum sample collected within an acceptable day range.

‡Non-inferiority for GMTs is defined as statistically less than a 2-fold decrease.

The estimated GMT, fold difference, associated confidence intervals, and p-values are based on a statistical analysis model.

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.

n = Number of subjects contributing to the analysis.

CI = Confidence interval; GMT = Geometric mean titer; mMU = Milli Merck units; cLIA = 9 valent Competitive Luminex immunoassay.

The above non-inferiority analysis served to confirm the choice of dose for the continuation into part B (Efficacy part) of the study.

Immunogenicity substudy

The primary immunogenicity objective for the immunogenicity substudy was to demonstrate that the 9vHPV vaccine induces non-inferior GMTs for anti-HPV 6, 11, 16, and 18 compared to qHPV vaccine. The secondary immunogenicity objectives for the immunogenicity substudy were to demonstrate that the 9vHPV vaccine is

immunogenic with respect to HPV types 31, 33, 45, 52, and 58, to demonstrate that the 9vHPV vaccine induces non-inferior immune responses with respect to seroconversion percentages for HPV Types 6, 11, 16, and 18 compared to the qHPV vaccine, and to evaluate the persistence of anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 immune responses generated by the 9vHPV vaccine.

Table 28 presents a summary of the per-protocol (PPI) observed anti-HPV 6, anti-HPV 11, anti-HPV 16, anti-HPV 18, anti-HPV 31, anti-HPV 33, anti-HPV 45, anti-HPV 52, and anti-HPV 58 GMTs from Day 1 until Month 42, with associated 95% CI's, by vaccination group. The observed GMTs in the All (HPV Type-specific) Naïve Subjects with Serology (ANSS) analysis population are generally consistent with those observed in the PPI population.

In order to address the primary immunogenicity objective of immunogenicity substudy, GMTs at 4 weeks Post-dose 3 were compared between the qHPV vaccine group and the selected 9vHPV vaccine group for use in efficacy analyses. A statistical analysis was conducted (at 1-sided α=0.025 level) to assess whether or not anti-HPV 6, 11, 16 and 18 cLIA GMTs at 4 weeks Post-dose 3 in subjects vaccinated with selected 9vHPV vaccine were non-inferior to anti-HPV 6, 11, 16 and 18 cLIA GMTs at 4 weeks Post-dose 3 in subjects vaccinated with qHPV vaccine.

Table 29. Summary of Anti-HPV cLIA Geometric Mean Titres by Vaccination Group (Per-Protocol Immunogenicity Population PPI - Immunogenicity Substudy)

	cLIA Assay			
	9vHPV Vaccine (N=6,792)		qHPV Vaccine (N=6,795)	
Anti-HPV	n	GMT (95% CI)	n	GMT (95% CI)
Anti-HPV 6				
Day 1	3,993	< 16 (<16, <16)	3,975	< 16 (<16, <16)
Month 3	788	734.0 (692.8, 777.7)	761	719.6 (678.5, 763.2)
Month 7	3,993	893.1 (871.7, 915.1)	3,975	875.2 (854.2, 896.8)
Month 12	800	330.6 (312.2, 350.1)	781	319.4 (301.4, 338.6)
Month 24	715	208.6 (195.5, 222.7)	690	205.1 (191.9, 219.1)
Month 36	685	163.9 (153.0, 175.6)	666	158.9 (148.2, 170.4)
Month 42	692	147.2 (137.3, 157.8)	675	144.3 (134.5, 154.8)
Anti-HPV 11				
Day 1	3,995	< 6 (<6, <6)	3,982	< 6 (<6, <6)
Month 3	790	529.1 (499.7, 560.1)	762	678.3 (640.1, 718.9)
Month 7	3,995	666.3 (649.6, 683.4)	3,982	830.0 (809.2, 851.4)
Month 12	810	212.4 (200.1, 225.6)	788	264.5 (248.9, 281.1)
Month 24	763	123.3 (115.8, 131.2)	735	148.1 (138.9, 157.8)
Month 36	690	89.6 (83.3, 96.3)	671	110.9 (103.1, 119.4)
Month 42	696	84.9 (79.0, 91.3)	677	104.0 (96.7, 111.9)
Anti-HPV 16				
Day 1	4,032	< 12 (<12, <12)	4,062	< 12 (<12, <12)
Month 3	794	2,435.8 (2,303.5, 2,575.6)	785	2,475.1 (2,340.0, 2,618.0)
Month 7	4,032	3,131.1 (3,057.1, 3,206.9)	4,062	3,156.6 (3,082.3, 3,232.7)
Month 12	819	1,041.7 (979.9, 1,107.4)	805	1,031.6 (969.9, 1,097.3)
Month 24	778	520.7 (484.7, 559.4)	759	508.0 (472.5, 546.3)
Month 36	695	386.5 (356.3, 419.4)	689	387.1 (356.7, 420.1)
Month 42	709	346.8 (319.3, 376.7)	690	362.9 (333.8, 394.6)

Anti-HPV	cLIA Assay			
	9vHPV Vaccine (N=6,792)		qHPV Vaccine (N=6,795)	
	n	GMT (95% CI)	n	GMT (95% CI)
Anti-HPV 18				
Day 1	4,539	< 8 (<8, <8)	4,541	< 8 (<8, <8)
Month 3	908	470.8 (442.8, 500.7)	877	371.0 (348.5, 395.0)
Month 7	4,539	804.6 (782.7, 827.1)	4,541	678.7 (660.2, 697.7)
Month 12	929	198.6 (184.9, 213.4)	901	160.2 (148.9, 172.2)
Month 24	886	86.0 (79.0, 93.6)	847	68.1 (62.4, 74.3)
Month 36	789	78.5 (71.9, 85.6)	768	62.4 (57.1, 68.1)
Month 42	806	70.8 (64.8, 77.3)	770	60.4 (55.2, 66.1)
Anti-HPV 31				
Day 1	4,466	< 4 (<4, <4)	4,377	< 4 (<4, <4)
Month 3	881	437.6 (406.7, 470.8)	838	6.3 (5.8, 6.7)
Month 7	4,466	658.4 (636.7, 680.9)	4,377	9.7 (9.4, 10.1)
Month 12	909	196.5 (183.5, 210.4)	858	4.1 (<4, 4.4)
Month 24	863	101.9 (94.9, 109.5)	805	< 4 (<4, <4)
Month 36	772	72.7 (67.5, 78.4)	724	< 4 (<4, <4)
Month 42	783	70.4 (65.3, 75.9)	730	< 4 (<4, <4)
Anti-HPV 33				
Day 1	4,702	< 4 (<4, <4)	4,691	< 4 (<4, <4)
Month 3	937	287.8 (272.9, 303.5)	893	< 4 (<4, <4)
Month 7	4,702	415.9 (405.6, 426.4)	4,691	< 4 (<4, <4)
Month 12	958	126.2 (119.9, 132.9)	921	< 4 (<4, <4)
Month 24	909	65.3 (61.7, 69.0)	868	< 4 (<4, <4)
Month 36	813	46.8 (44.0, 49.8)	785	< 4 (<4, <4)
Month 42	835	44.3 (41.6, 47.1)	789	< 4 (<4, <4)
Anti-HPV 45				
Day 1	4,792	< 3 (<3, <3)	4,750	< 3 (<3, <3)
Month 3	956	160.4 (151.7, 169.7)	910	< 3 (<3, <3)
Month 7	4,792	252.8 (246.2, 259.6)	4,750	< 3 (<3, <3)
Month 12	976	69.2 (65.4, 73.3)	937	< 3 (<3, <3)
Month 24	928	33.0 (31.0, 35.0)	882	< 3 (<3, <3)
Month 36	835	22.9 (21.4, 24.4)	800	< 3 (<3, <3)
Month 42	846	21.1 (19.8, 22.5)	802	< 3 (<3, <3)
Anti-HPV 52				
Day 1	4,455	< 3 (<3, <3)	4,335	< 3 (<3, <3)
Month 3	895	241.3 (229.7, 253.4)	835	< 3 (<3, <3)
Month 7	4,455	379.7 (371.6, 388.0)	4,335	< 3 (<3, <3)
Month 12	916	118.9 (113.0, 125.0)	857	< 3 (<3, <3)
Month 24	867	57.9 (54.7, 61.2)	809	< 3 (<3, <3)
Month 36	777	47.9 (45.0, 50.9)	732	< 3 (<3, <3)
Month 42	791	43.2 (40.6, 46.0)	735	< 3 (<3, <3)
Anti-HPV 58				
Day 1	4,486	< 4 (<4, <4)	4,446	< 4 (<4, <4)
Month 3	884	281.1 (265.3, 297.7)	863	< 4 (<4, <4)
Month 7	4,486	482.5 (469.9, 495.3)	4,446	< 4 (<4, <4)
Month 12	905	153.3 (145.5, 161.6)	883	< 4 (<4, <4)
Month 24	852	80.3 (75.7, 85.3)	835	< 4 (<4, <4)
Month 36	765	55.0 (51.4, 58.8)	747	< 4 (<4, <4)
Month 42	784	52.0 (48.7, 55.6)	756	< 4 (<4, <4)

The per-protocol immunogenicity population includes all subjects who were not general protocol violators, received all 3 vaccinations within acceptable day ranges, were seronegative at Day 1 and PCR negative Day 1 through Month 7 for the relevant HPV type, and had a Month 7 serum sample collected within an acceptable day range.
N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects contributing to the analysis.
9vHPV = Nine-Valent Human papillomavirus (Types 6, 11, 16, 18, 31, 33, 45, 52, 58) Recombinant Vaccine; qHPV = Quadrivalent Human papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine
CI = Confidence interval; cLIA = Competitive Luminex immunoassay; GMT = Geometric mean titre; IgG = Immunoglobulin G; mMU = Milli Merck units.

Concerning anti-HPV immunogenicity up to Month 42, comparable seropositivity rates (cLIA) were noted between 9vHPV and qHPV groups for each of 4 original vaccine HPV types. For 5 new vaccine HPV types the seropositivity rates were clearly higher in 9vHPV group than in qHPV group. At Month 42, percentage of seropositivity (cLIA assay) in 9vHPV recipients remained high and was 93.6% (95%CL: 91.7, 95.2) for HPV-31, 94.6% (95%CI: 92.9, 96.0) for HPV-33, 78.8% (95%CI: 75.9, 81.5) for HPV-45, 95.2% (95%CI: 93.5, 96.6) for HPV-52, and 94.4% (95%CI: 92.5, 95.9) for HPV-58.

Anti-HPV GMTs (cLIA) were highest at Month 7 and declined drastically at Month 12, and appeared to reach plateau at Month 36 for each of the 9 vaccine types. Notably, anti-HPV 11 cLIA titres were consistently lower from Month 3 through Month 42 in 9vHPV group than in qHPV group.

Table 29 presents the results of the per-protocol analysis of non-inferiority comparing Month 7 cLIA GMTs between subjects who received the selected 9vHPV vaccine and subjects who received qHPV vaccine. The statistical criterion for non-inferiority with respect to GMT required that the lower bound of the 95% CI for the fold difference in anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 GMTs (selected 9vHPV vaccine/qHPV vaccine) was above 0.67, to exclude a decrease of 1.5-fold or more. The table shows that the non-inferiority hypothesis of GMT responses for each of the HPV Types 6, 11, 16, and 18 in the selected 9vHPV vaccine relative to GMT responses in the qHPV vaccine group at 4 weeks Post-dose 3 was met in the PPI population with p-values < 0.001.

The non-inferiority criteria for GMT responses for each of the HPV Types 6, 11, 16, and 18 in the 9vHPV vaccine relative to GMT responses in the qHPV vaccine group at 4 weeks Post-dose 3 were met in the ANSS population with p-values < 0.001.

Table 30. Statistical Analysis of Non-Inferiority Comparing Month 7 HPV cLIA Geometric Mean Titres (HPV-types 6, 11, 16 and 18) Between Subjects Who Received 9vHPV Vaccine and Subjects Who Received qHPV Vaccine (Per-Protocol Immunogenicity Population - Immunogenicity Substudy)

	Comparison Group					
	9vHPV Vaccine (Comparison Group A) (N = 6,792)		qHPV Vaccine (Comparison Group B) (N = 6,795)		Estimated Fold Difference Group A / Group B	p-Value for
Assay (cLIA)	n	Estimated GMT (mMU/mL)	n	Estimated GMT (mMU/mL)	(95% CI)	Non-Inferiority‡
Anti-HPV 6	3,993	893.1	3,975	875.2	1.02 (0.99, 1.06)	<0.001
Anti-HPV 11	3,995	666.3	3,982	830.0	0.80 (0.77, 0.83)	<0.001
Anti-HPV 16	4,032	3,131.1	4,062	3,156.6	0.99 (0.96, 1.03)	<0.001
Anti-HPV 18	4,539	804.6	4,541	678.7	1.19 (1.14, 1.23)	<0.001
Overall conclusion: The non-inferiority criteria was met for all 4 HPV types.						

†The per-protocol immunogenicity population includes all subjects who were not general protocol violators, received all 3 vaccinations within acceptable day ranges, were seronegative at Day 1 and PCR negative Day 1 through Month 7 for the relevant HPV type(s), and had a Month 7 serum sample collected within an acceptable day range.

‡Non-inferiority for GMTs is defined as statistically less than a 1.5-fold decrease.

The estimated GMT, fold difference, associated confidence intervals, and p-values are based on a statistical analysis model.

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.

n = Number of subjects contributing to the analysis.

CI = Confidence interval; GMT = Geometric mean titer; mMU = Milli Merck units; cLIA = 9 valent Competitive Luminex immunoassay.

The differences between the two groups were small, and it is agreed that non-inferiority of GMTs has been demonstrated.

In order to address a secondary immunogenicity objective of the immunogenicity substudy, seroconversion percentages at 4 weeks Post-dose 3 were compared between the qHPV vaccine group and the selected 9vHPV vaccine group for use in efficacy analyses. A statistical analysis was conducted (at 1-sided α=0.025 level) to assess whether or not seroconversion percentages at 4 weeks Post-dose 3 for HPV types 6, 11, 16, and 18 in subjects vaccinated with selected 9vHPV vaccine were non-inferior to the seroconversion percentages at 4 weeks Post-dose 3 for HPV types 6, 11, 16, and 18 in subjects vaccinated with qHPV vaccine. The statistical criterion for non-inferiority with respect to seroconversion percentages required that the lower bound of the

95% CI for the percentage point difference in anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 seroconversion percentages (9vHPV vaccine-qHPV vaccine) was above -5 percentage points. The non-inferiority hypothesis of seroconversion percentages for each of the HPV Types 6, 11, 16, and 18 in the selected 9vHPV vaccine relative to seroconversion percentages in the qHPV vaccine group at 4 weeks Post-dose 3 was met in the PPI population with p-values < 0.001. Numerically the differences of seroconversion percentages between the vaccine groups were close to 0 and all related confidence intervals covered 0 and no confidence interval covered -5.

In order to address a secondary immunogenicity objective of the immunogenicity substudy, seroconversion percentages at 4 weeks Post-dose 3 for the selected 9vHPV vaccine group for use in efficacy analyses were analysed. A statistical analysis was conducted (at 1-sided α=0.025 level) to assess whether or not seroconversion percentages at 4 weeks Post-dose 3 for HPV types 31, 33, 45, 52 and 58 in subjects vaccinated with selected 9vHPV vaccine were acceptable (acceptability was defined as the lower bound of the 95% confidence interval is greater than 90%).

Table 30 presents the results of the per-protocol analysis of acceptability for Month 7 seroconversion percentages for HPV types 31, 33, 45, 52 and 58 for subjects who received the selected 9vHPV vaccine. The statistical criterion for acceptability with respect to seroconversion percentages required that the lower bound of the 95% CI for the percentage point difference in anti-HPV 31, anti-HPV 33, anti-HPV 33, anti-HPV 52, and anti-HPV 58 seroconversion percentages was above 90 percentage points. The table shows that the acceptability hypothesis of seroconversion percentages for each of the HPV Types 31, 33, 45, 52, and 58 in the selected 9vHPV vaccine at 4 weeks Post-dose 3 was met in the PPI population with p-values < 0.001. The confidence intervals for the seroconversion 4 weeks Post-dose 3 were above 99% for all HPV types.

Table 31. Statistical Analysis of Acceptability of Anti-HPV cLIA Seropositivity Percentages for HPV-types 31, 33, 45, 52 and 58 at Month 7 (Per-Protocol Immunogenicity Population - Immunogenicity Sub-study)

HPV-Type	9vHPV Vaccine (N=6,792)				
		Seropositivity			
	n	m	Percent[‡]	95% CI	p-Value[‡]
Anti-HPV 31	4,466	4,457	99.8%	(99.6%, 99.9%)	<0.001
Anti-HPV 33	4,702	4,689	99.7%	(99.5%, 99.9%)	<0.001
Anti-HPV 45	4,792	4,773	99.6%	(99.4%, 99.8%)	<0.001
Anti-HPV 52	4,455	4,446	99.8%	(99.6%, 99.9%)	<0.001
Anti-HPV 58	4,486	4,476	99.8%	(99.6%, 99.9%)	<0.001
Conclusion: Acceptable HPV 31, 33, 45, 52, 58 seroconversion percentages.					

[‡] Percent represents proportion of subjects with anti-HPV serum levels ≥ 10, 8, 8, 8, and 8 mMU/mL for HPV types 31, 33, 45, 52, and 58, respectively.
[‡] A p-value <= 0.025 corresponds to a lower bound of the 2-sided 95% confidence interval of > 0.90 and supports the conclusion that the given anti-HPV seroconversion percentage is acceptable.
The per-protocol immunogenicity population includes all subjects who were not general protocol violators, received all 3 vaccinations within acceptable day ranges, were seronegative at Day 1 and PCR negative Day 1 through Month 7 for the relevant HPV type(s), and had a Month 7 serum sample collected within an acceptable day range.
N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects contributing to the analysis.
m = Number of subjects seropositive to the relevant HPV type(s).
CI = Confidence interval; cLIA = 9 valent Competitive Luminex immunoassay; GMT = Geometric mean titer.

In addition to the above immunogenicity analyses, the MAH also presented the results of PBNA analyses in a subset of the immunogenicity population. The PBNA was requested by the CHMP in a Scientific Advice. The results were in agreement with the cLIA results, and thus considered supportive of the immunogenicity conclusions. A strong correlation between the PBNA and cLIA was also demonstrated in the analysis (data not shown). The PBNA was only used for HPV 16 and 18, which are considered the most important types to demonstrate non-inferiority for a female population.

Immunological correlates of protection

It is acknowledged that there is no established correlate of protection. Within the range of anti-HPV 6, anti-HPV 11, anti-HPV 16, anti-HPV 18, anti-HPV 31, anti-HPV 33, anti-HPV 45, anti-HPV 52, and anti-HPV 58 responses observed in this study (lower quartiles and upper quartiles), there was no apparent association between increased risk of HPV 6-, 11-, 16-, 18-, 31-, 33-, 45-, 52-, or 58-related infection and disease and lower

anti-HPV 6, anti-HPV 11, anti-HPV 16, anti-HPV 18, anti-HPV 31, anti-HPV 33, anti-HPV 45, anti-HPV 52, and anti-HPV 58 cLIA titres. This indicates that even subjects with lower antibody responses exhibit a high degree of protection from HPV 6-, 11-, 16-, 18-, 31-, 33-, 45-, 52-, or 58-related infection and disease.

Study 002

The immunogenicity results from study 002 are presented according to the two sub-studies: adolescent-adult immunobridging and manufacturing lot consistency.

Adolescent-Adult Immunobridging Substudy

To test the primary and secondary immunogenicity hypotheses, the immune responses among 9- to 15-year-old girls were compared to the immune responses among 16- to 26-year-old women, and the immune responses among 9- to 15-year-old boys were compared to the immune responses among 16- to 26-year-old women. These comparisons were performed for both GMTs and the proportions of subjects who seroconverted based on the anti-HPV cLIAs.

Table 31 displays the statistical analysis of non-inferiority of Month 7 HPV cLIA GMTs comparing 9- to 15-year-old girls to 16- to 26-year-old young women for each vaccine HPV type in the PPI population. For each HPV type, the statistical criterion for success required that the lower confidence bound exceed 0.67. The lower bound exceeded 0.67 for all HPV types, with p-values <0.001. Therefore, the criterion was met, supporting the conclusion that GMTs in 9- to 15-year-old girls are non-inferior to those in 16- to 26-year-old young women. Numerically, the GMT ratios for HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 ranged from 1.83 to 2.62, with related lower bound of confidence intervals exceeding 1.

Table 32. Statistical Analysis of Non-Inferiority of Month 7 HPV cLIA Geometric Mean titres Comparing 9- to 15-Year-Old Females (Lot 1) and 16- to 26-Year-Old Females (Lot 1) (Per-Protocol Immunogenicity Population)

	Comparison Group					
	9- to 15-Year-Old Females (Lot 1) (Comparison Group A) (N = 646)		16- to 26-Year-Old Females (Comparison Group B) (N = 468)		Estimated Fold Difference Group A / Group B (95% CI)	p-Value for Non-Inferiority[†]
Assay (cLIA)	n	Estimated GMT (mMU/mL)	n	Estimated GMT (mMU/mL)		
Anti-HPV 6	517	1,715.4	328	900.8	1.90 (1.70, 2.14)	<0.001
Anti-HPV 11	517	1,295.1	332	706.6	1.83 (1.63, 2.06)	<0.001
Anti-HPV 16	529	6,979.8	329	3,522.6	1.98 (1.77, 2.22)	<0.001
Anti-HPV 18	531	2,153.7	345	882.7	2.44 (2.13, 2.80)	<0.001
Anti-HPV 31	522	1,891.6	340	753.9	2.51 (2.21, 2.85)	<0.001
Anti-HPV 33	534	980.4	354	466.8	2.10 (1.87, 2.36)	<0.001
Anti-HPV 45	534	714.4	368	272.2	2.62 (2.27, 3.03)	<0.001
Anti-HPV 52	533	932.9	337	419.6	2.22 (1.97, 2.51)	<0.001
Anti-HPV 58	531	1,286.7	332	590.5	2.18 (1.93, 2.45)	<0.001

Overall conclusion: The non-inferiority criteria was met for all 9 HPV types.

[†] The noninferiority criterion for endpoints reported in this table is defined as statistically less than 1.5-fold decrease in Group A compared to Group B. Noninferiority of GMT in Group A relative to Group B is demonstrated if the lower limit of the 95% CI for the fold difference is greater than 0.67.

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.

n = Number of subjects contributing to the analysis.

CI = Confidence interval; GMT = Geometric mean titer; mMU = Milli Merck units; cLIA = 9 valent Competitive Luminex immunoassay.

Table 32 displays the statistical analysis of non-inferiority of Month 7 HPV cLIA GMTs comparing 9- to 15-year-old boys to 16- to 26-year-old young women for each vaccine HPV type in the PPI population. The statistical criterion for the comparison of 9-to 15-year-old boys to 16- to 26-year-old young women was

analogous to that for 9- to 15-year-old girls to 16- to 26-year-old young women. The lower bound exceeded 0.67 for all HPV types, with p-values < 0.001. Therefore, the criterion was met, supporting the conclusion that GMTs in 9- to 15-year-old boys are non-inferior to those in 16- to 26-year-old young women. Numerically the GMT ratios for HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 ranged from 2.10 to 3.33 with related lower bound of confidence intervals exceeding 1.

The results from the analysis in the ANSS population were similar to the results from the per-protocol analysis.

Table 33. Statistical Analysis of Non-Inferiority of Month 7 HPV cLIA Geometric Mean Titres Comparing 9- to 15-Year-Old Males (Lot 1) and 16- to 26-Year-Old Females (Lot 1) (Per-Protocol Immunogenicity Population)

	Comparison Group					
	9- to 15-Year-Old Males (Comparison Group A) (N = 666)		16- to 26-Year-Old Females (Comparison Group B) (N = 468)		Estimated Fold Difference Group A / Group B (95% CI)	p-Value for Non-Inferiority[†]
Assay (cLIA)	n	Estimated GMT (mMU/mL)	n	Estimated GMT (mMU/mL)		
Anti-HPV 6	559	2,084.7	328	900.8	2.31 (2.07, 2.59)	<0.001
Anti-HPV 11	559	1,487.1	332	706.6	2.10 (1.88, 2.36)	<0.001
Anti-HPV 16	569	8,628.9	329	3,522.6	2.45 (2.19, 2.74)	<0.001
Anti-HPV 18	567	2,822.8	345	882.7	3.20 (2.80, 3.65)	<0.001
Anti-HPV 31	564	2,221.2	340	753.9	2.95 (2.60, 3.34)	<0.001
Anti-HPV 33	567	1,198.7	354	466.8	2.57 (2.29, 2.88)	<0.001
Anti-HPV 45	570	907.0	368	272.2	3.33 (2.89, 3.84)	<0.001
Anti-HPV 52	568	1,037.8	337	419.6	2.47 (2.19, 2.79)	<0.001
Anti-HPV 58	566	1,567.7	332	590.5	2.66 (2.37, 2.98)	<0.001
Overall conclusion: The non-inferiority criteria was met for all 9 HPV types.						

[†] The noninferiority criterion for endpoints reported in this table is defined as statistically less than 1.5-fold decrease in Group A compared to Group B. Noninferiority of GMT in Group A relative to Group B is demonstrated if the lower limit of the 95% CI for the fold difference is greater than 0.67.

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.

n = Number of subjects contributing to the analysis.

CI = Confidence interval; GMT = Geometric mean titer; mMU = Milli Merck units; cLIA = 9 valent Competitive Luminex immunoassay.

The GMTs in girls and boys 9-15 years were clearly non-inferior to the GMTs in the efficacy population, i.e. women 16-26 years of age.

Table 33 displays the statistical analysis of non-inferiority comparing 9- to 15-year-old girls to 16- to 26-year-old young women with regard to the proportion who became seropositive to each vaccine HPV type by Month 7 in the PPI population. The statistical criterion for success required that the lower confidence bound exceed -5.0 percentage points. The lower bound exceeded -5.0 percentage points for all HPV types, with p-values <0.001. Therefore, the criterion was met, supporting the conclusion that the proportions of 9- to 15-year-old girls who became seropositive to vaccine HPV types were non-inferior to those observed in 16- to 26-year-old young women.

Table 34. Statistical Analysis of Non-Inferiority With Regard to the Proportions of 9- to 15-Year-Old Females (Lot 1) and 16- to 26-Year-Old Females (Lot 1) Who Became Seropositive to Vaccine HPV Types at Month 7 (Per-Protocol Immunogenicity Population)

	9vHPV Vaccine 9- to 15-Year-Old Females (Lot 1) (Group A) (N = 646)			9vHPV Vaccine 16- to 26-Year-Old Females (Group B) (N = 468)			Estimated Percentage Point Difference Group A - Group B (95% CI)[§]	p-Value for Non-Inferiority[‡]
Anti-HPV cLIA Response	n	m	Seroconversion (%)	n	m	Seroconversion (%)		
HPV 6 cLIA ≥30 mMU/mL	517	516	99.8	328	327	99.7	0.1 (-0.8, 1.5)	<0.001
HPV 11 cLIA ≥16 mMU/mL	517	517	100.0	332	332	100.0	0.0 (-0.7, 1.2)	<0.001
HPV 16 cLIA ≥20 mMU/mL	529	529	100.0	329	329	100.0	0.0 (-0.7, 1.2)	<0.001
HPV 18 cLIA ≥24 mMU/mL	531	530	99.8	345	344	99.7	0.1 (-0.8, 1.5)	<0.001
HPV 31 cLIA ≥10 mMU/mL	522	522	100.0	340	339	99.7	0.3 (-0.4, 1.7)	<0.001
HPV 33 cLIA ≥8 mMU/mL	534	534	100.0	354	353	99.7	0.3 (-0.4, 1.6)	<0.001
HPV 45 cLIA ≥8 mMU/mL	534	533	99.8	368	366	99.5	0.4 (-0.6, 1.8)	<0.001
HPV 52 cLIA ≥8 mMU/mL	533	533	100.0	337	336	99.7	0.3 (-0.4, 1.7)	<0.001
HPV 58 cLIA ≥8 mMU/mL	531	531	100.0	332	332	100.0	0.0 (-0.7, 1.2)	<0.001

[‡] The noninferiority criterion for endpoints reported in this table is defined as statistically less than 5 percentage points decrease in Group A compared to Group B. Noninferiority of seroconversion rates in Group A relative to Group B is demonstrated if the lower limit of the 95% CI for the percentage point difference is greater than -5.

[§] Point and interval estimates for the difference of proportions were obtained using the methods developed by Miettinen and Nurminen.

Seroconversion was defined as changing serostatus from seronegative to seropositive. Cutoff values for HPV seropositivity are ≥30, 16, 20, 24, 10, 8, 8, 8, and 8 mMU/mL for HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 respectively.

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.

n = Number of subjects with evaluable serology data and are eligible for the indicated analysis population.

m = Number of subjects who had seroconversion.

CI = Confidence interval; cLIA = Competitive Luminex immunoassay; HPV = Human papillomavirus; mMU = Milli Merck units.

Table 34 displays statistical analyses of non-inferiority comparing 9- to 15-year-old boys to 16- to 26-year-old young women with regard to the proportion who became seropositive to each HPV type by Month 7 in the PPI population. The statistical criterion for the comparison of 9- to 15-year-old boys to 16- to 26-year-old young women was analogous to that for 9- to 15-year-old girls to 16- to 26-year-old young women. The lower bound exceeded -5.0 percentage points for all HPV types, with p-values <0.001. Therefore, the criterion was met, supporting the conclusion that the proportions of 9- to 15-year-old boys who became seropositive to vaccine HPV types by Month 7 were non-inferior to those observed in 16- to 26-year-old young women.

Table 35. Statistical Analysis of Non-Inferiority With Regard to the Proportions of 9- to 15-Year-Old Males (Lot 1) and 16- to 26-Year-Old Females (Lot 1) Who Became Seropositive to Vaccine HPV Types at Month 7 (Per-Protocol Immunogenicity Population)

	9vHPV Vaccine 9- to 15-Year-Old Males (Group A) (N = 666)			9vHPV Vaccine 16- to 26-Year-Old Females (Group B) (N = 468)			Estimated Percentage Point Difference Group A - Group B (95% CI)[§]	p-Value for Non-Inferiority[‡]
Anti-HPV cLIA Response	n	m	Seroconversion (%)	n	m	Seroconversion (%)		
HPV 6 cLIA ≥30 mMU/mL	559	558	99.8	328	327	99.7	0.1 (-0.7, 1.5)	<0.001
HPV 11 cLIA ≥16 mMU/mL	559	559	100.0	332	332	100.0	0.0 (-0.7, 1.2)	<0.001
HPV 16 cLIA ≥20 mMU/mL	569	569	100.0	329	329	100.0	0.0 (-0.7, 1.2)	<0.001
HPV 18 cLIA ≥24 mMU/mL	567	567	100.0	345	344	99.7	0.3 (-0.4, 1.6)	<0.001
HPV 31 cLIA ≥10 mMU/mL	564	564	100.0	340	339	99.7	0.3 (-0.4, 1.7)	<0.001
HPV 33 cLIA ≥8 mMU/mL	567	567	100.0	354	353	99.7	0.3 (-0.4, 1.6)	<0.001
HPV 45 cLIA ≥8 mMU/mL	570	570	100.0	368	366	99.5	0.5 (-0.1, 2.0)	<0.001
HPV 52 cLIA ≥8 mMU/mL	568	568	100.0	337	336	99.7	0.3 (-0.4, 1.7)	<0.001
HPV 58 cLIA ≥8 mMU/mL	566	566	100.0	332	332	100.0	0.0 (-0.7, 1.2)	<0.001

[‡] The noninferiority criterion for endpoints reported in this table is defined as statistically less than 5 percentage points decrease in Group A compared to Group B. Noninferiority of seroconversion rates in Group A relative to Group B is demonstrated if the lower limit of the 95% CI for the percentage point difference is greater than -5.

[§] Point and interval estimates for the difference of proportions were obtained using the methods developed by Miettinen and Nurminen.

Seroconversion was defined as changing serostatus from seronegative to seropositive. Cutoff values for HPV seropositivity are ≥30, 16, 20, 24, 10, 8, 8, 8, and 8 mMU/mL for HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 respectively.

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.

n = Number of subjects with evaluable serology data and are eligible for the indicated analysis population.

m = Number of subjects who had seroconversion.

CI = Confidence interval; cLIA = Competitive Luminex immunoassay; HPV = Human papillomavirus; mMU = Milli Merck units.

The analysis of proportion of seroconverters supports the non-inferiority analysis of GMTs.

Table 35 shows the results from the End of study report of protocol 002 (V503-002-10 Study Extension) in boys and girls up to 36 months post-vaccination (dose 1). Anti-HPV response induced by 9vHPV to each of the vaccine HPV types generally persisted through Month 36 post-vaccination onset. A similar anti-HPV response kinetic as seen in V503-001 (extension study of protocol 001) was noted for 9-15 year of age preadolescents and adolescents. Safety results of this report further indicated that a 3-dose regimen of 9vHPV vaccine was generally well tolerated through Month 36 post-vaccination onset in (pre)adolescent girls and boys.

Table 36. Summary of Anti-HPV cLIA Geometric Mean Titres by Age Group (Per-Protocol Immunogenicity Population)

		9vHPV Vaccine								
		9 to 12 Years of Age			13 to 15 Years of Age			Total		
Assay (cLIA)	Time Point	n	GMT (mMU/mL)	95% CI	n	GMT (mMU/mL)	95% CI	n	GMT (mMU/mL)	95% CI
Anti-HPV 6	Day 1	1,430	< 16	(<16, <16)	726	< 16	(<16, <16)	2,156	< 16	(<16, <16)
	Month 07	1,430	2,044.5	(1,954.6, 2,138.7)	726	1,404.6	(1,318.6, 1,496.2)	2,156	1,801.7	(1,735.6, 1,870.4)
	Month 12	617	696.4	(651.2, 744.6)	311	581.1	(528.7, 638.6)	928	655.4	(620.4, 692.4)
	Month 24	591	340.0	(317.3, 364.4)	295	297.6	(269.8, 328.3)	886	325.3	(307.3, 344.2)
	Month 36	577	268.7	(249.7, 289.1)	287	237.7	(214.3, 263.8)	864	258.0	(243.0, 273.9)
Anti-HPV 11	Day 1	1,430	< 6	(<6, <6)	726	< 6	(<6, <6)	2,156	< 6	(<6, <6)
	Month 07	1,430	1,494.2	(1,427.5, 1,564.0)	726	1,056.9	(991.3, 1,126.8)	2,156	1,329.8	(1,280.4, 1,381.0)
	Month 12	619	453.9	(421.2, 489.2)	315	375.2	(337.8, 416.7)	934	425.7	(400.4, 452.5)
	Month 24	593	201.3	(185.9, 218.0)	296	171.3	(153.1, 191.8)	889	190.8	(178.7, 203.6)
	Month 36	583	158.0	(145.6, 171.5)	291	138.9	(123.7, 156.0)	874	151.4	(141.6, 161.9)
Anti-HPV 16	Day 1	1,459	< 12	(<12, <12)	737	< 12	(<12, <12)	2,196	< 12	(<12, <12)
	Month 07	1,459	8,545.2	(8,183.9, 8,922.5)	737	5,669.2	(5,334.9, 6,024.5)	2,196	7,445.9	(7,181.7, 7,719.8)
	Month 12	629	2,901.3	(2,720.0, 3,094.7)	320	2,200.4	(2,010.1, 2,408.7)	949	2,643.0	(2,506.1, 2,787.3)
	Month 24	603	1,273.7	(1,179.6, 1,375.4)	301	954.7	(856.3, 1,064.3)	904	1,157.1	(1,086.1, 1,232.8)
	Month 36	593	986.2	(907.7, 1,071.4)	295	755.1	(671.3, 849.2)	888	902.5	(842.9, 966.2)
Anti-HPV 18	Day 1	1,467	< 8	(<8, <8)	741	< 8	(<8, <8)	2,208	< 8	(<8, <8)
	Month 07	1,467	2,653.1	(2,520.3, 2,792.9)	741	1,625.0	(1,511.8, 1,746.8)	2,208	2,250.7	(2,156.1, 2,349.4)
	Month 12	629	703.3	(644.7, 767.3)	320	494.9	(438.0, 559.1)	949	624.7	(581.6, 671.1)
	Month 24	603	296.0	(270.0, 324.5)	301	203.9	(179.0, 232.2)	904	261.4	(242.3, 282.0)
	Month 36	593	229.5	(208.3, 252.9)	295	162.5	(141.6, 186.4)	888	204.6	(188.9, 221.6)
Anti-HPV 31	Day 1	1,451	< 4	(<4, <4)	730	< 4	(<4, <4)	2,181	< 4	(<4, <4)
	Month 07	1,451	2,288.1	(2,179.1, 2,402.6)	730	1,446.0	(1,349.8, 1,549.0)	2,181	1,962.3	(1,883.8, 2,044.1)
	Month 12	626	715.2	(659.3, 775.7)	317	496.6	(442.9, 556.7)	943	632.6	(591.5, 676.5)
	Month 24	599	319.3	(291.5, 349.7)	298	207.4	(182.3, 236.0)	897	276.6	(256.5, 298.3)
	Month 36	589	261.9	(238.7, 287.4)	292	181.3	(158.9, 206.9)	881	231.9	(214.7, 250.3)
Anti-HPV 33	Day 1	1,460	< 4	(<4, <4)	744	< 4	(<4, <4)	2,204	< 4	(<4, <4)
	Month 07	1,460	1,134.0	(1,084.5, 1,185.7)	744	790.4	(742.5, 841.3)	2,204	1,003.9	(967.4, 1,041.7)
	Month 12	622	356.5	(330.9, 384.0)	322	267.7	(241.4, 296.8)	944	323.3	(304.2, 343.6)
	Month 24	595	147.7	(135.6, 160.8)	303	109.6	(97.2, 123.5)	898	133.5	(124.5, 143.2)
	Month 36	586	117.1	(107.2, 127.8)	297	90.9	(80.3, 102.8)	883	107.5	(100.0, 115.5)
Anti-HPV 45	Day 1	1,472	< 3	(<3, <3)	745	< 3	(<3, <3)	2,217	< 3	(<3, <3)
	Month 07	1,472	917.1	(867.7, 969.4)	745	560.9	(518.9, 606.3)	2,217	777.4	(742.4, 814.2)
	Month 12	632	264.5	(240.4, 291.1)	322	162.7	(142.3, 186.0)	954	224.5	(207.4, 243.0)
	Month 24	605	106.8	(96.1, 118.6)	303	60.6	(52.2, 70.3)	908	88.4	(81.0, 96.5)
	Month 36	595	84.8	(76.1, 94.5)	297	49.3	(42.3, 57.5)	892	70.8	(64.7, 77.5)
Anti-HPV 52	Day 1	1,469	< 3	(<3, <3)	741	< 3	(<3, <3)	2,210	< 3	(<3, <3)
	Month 07	1,469	1,130.5	(1,078.7, 1,184.9)	741	755.0	(706.7, 806.6)	2,210	987.4	(949.5, 1,026.8)
	Month 12	633	329.6	(304.7, 356.4)	320	260.9	(233.7, 291.3)	953	304.7	(285.7, 324.9)
	Month 24	606	145.7	(134.4, 158.0)	301	117.2	(104.5, 131.4)	907	135.6	(126.8, 144.9)
	Month 36	596	113.3	(104.2, 123.1)	295	95.5	(84.8, 107.6)	891	107.0	(99.9, 114.7)
Anti-HPV 58	Day 1	1,461	< 4	(<4, <4)	735	< 4	(<4, <4)	2,196	< 4	(<4, <4)
	Month 07	1,461	1,538.7	(1,470.3, 1,610.3)	735	1,033.7	(969.5, 1,102.1)	2,196	1,346.9	(1,296.8, 1,398.9)
	Month 12	629	525.5	(488.4, 565.4)	319	390.9	(352.7, 433.2)	948	475.7	(447.9, 505.2)
	Month 24	602	223.0	(205.4, 242.0)	300	159.6	(142.1, 179.3)	902	199.5	(186.4, 213.5)
	Month 36	592	176.2	(161.5, 192.3)	295	130.3	(115.1, 147.4)	887	159.4	(148.3, 171.3)

n = Number of subjects contributing to the analysis.
CI = Confidence interval; cLIA = Competitive Luminex immunoassay; HPV = Human papillomavirus.

The results were in agreement with previously reported results, and did not raise concern regarding waning immunogenicity.

Manufacturing Lot Consistency Sub-study

The objective of the substudy is to demonstrate that 3 separate lots of 9vHPV vaccine induce similar immune responses, as measured by the serum GMTs to HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 at Week 4 post-dose 3 (month 7). The results of type-specific Month 7 GMT comparisons among subjects randomized to the 3 manufacturing lots of 9vHPV vaccine in the PPI population showed that, for each comparison, the lower bound of the 95% CI of GMT ratio between the comparison lots was greater than 0.5 and the upper bound was less than 2.0. Therefore, equivalence can be established in all 3 pairwise comparisons for each vaccine HPV type. Overall, for all HPV vaccine types, the Month 7 anti-HPV GMT responses from the 3 manufacturing lots of 9vHPV vaccine

were consistent. The secondary endpoint looked at percentage of subjects achieving seroconversion. These results demonstrate that for all vaccine components, the type-specific Month 7 seroconversion rates from the 3 manufacturing lots of 9vHPV vaccine were consistent.

Overall the lot-to-lot consistency is considered demonstrated in terms of immune responses in the target population.

Study 009/GDS01C

The main analysis was the non-inferiority comparison of post-dose 3 anti-HPV types 16 and 18 GMTs - 9vHPV versus qHPV vaccine. Table 36 summarizes the results. Antibody titres to each HPV type are determined by cLIA. The non-inferiority of the 9vHPV vaccine compared to qHPV vaccine was demonstrated for HPV16 and HPV18 since the lower bound of the two-sided 95% CI around the post-dose 3 GMT ratio (9vHPV vaccine/qHPV vaccine) was greater than 0.67 (2/3) for both HPV types.

Similar values of GMT were observed on the HPV specific ANSS and the estimate GMT ratio was almost identical to the one reported on the PPS.

Table 37. Non-Inferiority Comparison of Post-Dose 3 anti-HPV Types 16 and 18 GMTs -9vHPV versus qHPV Vaccine - HPV Specific Per Protocol Set

	9vHPV Vaccine (N=300)			qHPV Vaccine (N=300)				
Assay (cLIA)	n	GMT (mMU/mL)	[95% CI]	n	GMT (mMU/mL)	[95% CI]	Estimated GMT ratio 9vHPV / qHPV [95% CI] (a)	p-value for non-inferiority (b)
Anti-HPV 16	276	6739.5	[6134.5;7404.1]	270	6887.4	[6220.8;7625.5]	0.97 [0.85;1.11]	<0.001
Anti-HPV 18	276	1956.6	[1737.3;2203.7]	269	1795.6	[1567.2;2057.3]	1.08 [0.91;1.29]	<0.001

(a) Non-inferiority is achieved if the lower bound of the 2-sided 95% CI for the GMT ratio is greater than 0.67
(b) The estimated GMT ratio, associated confidence interval and p-value are based on an ANOVA model including group and age stratum as independent variables
cLIA=Competitive Luminex ImmunoAssay; CI=Confidence Interval; GMT=Geometric Mean Titer; mMU=Milli Merck units

The secondary objective concerned the post-dose 3 anti-HPV 6 and anti-HPV11 GMTs in subjects administered 9vHPV vaccine or qHPV vaccine. The results are presented in Table 37.

Similar results of post-dose 3 anti-HPV 6 and anti-HPV 11 GMTs were observed on the HPV specific ANSS.

Table 38. Comparison of Post-Dose 3 Anti-HPV Types 6 and 11 GMTs by Vaccination Group - HPV Specific Per Protocol Set

	9vHPV Vaccine (N=300)			qHPV Vaccine (N=300)			
Assay (cLIA)	n	GMT (mMU/mL)	[95% CI]	n	GMT (mMU/mL)	[95% CI]	Estimated GMT ratio 9vHPV / qHPV [95% CI] (1)
Anti-HPV 6	273	1679.4	[1518.9;1856.9]	261	1565.9	[1412.2;1736.3]	1.07 [0.93;1.23]
Anti-HPV 11	273	1315.6	[1183.8;1462.0]	261	1417.3	[1274.2;1576.5]	0.93 [0.80;1.08]

(1) The estimated GMT ratio and associated confidence interval are based on an ANOVA model including group as independent variables
cLIA=Competitive Luminex ImmunoAssay; CI=Confidence Interval; GMT=Geometric Mean Titre; mMU=Milli Merck units

The immune responses against the four common HPV types were very similar in the two groups, and non-inferiority was clearly demonstrated.

All subjects seroconverted to HPV types 6, 11, 16 and 18 with both vaccines.

GMTs were analysed according to age strata: 9-12 years old and 13-15 years old. The GMTs were numerically higher for younger girls and comparable in both vaccination groups. Similar results of post-dose 3 anti-HPV 6 and anti-HPV 11 GMTs were observed on the HPV specific ANSS.

Post-dose 3 anti-HPV 31, anti-HPV 33, anti-HPV 45, anti-HPV 52 and anti-HPV 58 GMTs are summarized in Table 38. All subjects seroconverted to the 9 HPV types after receiving the 3-dose schedule of the 9vHPV vaccine, except one subject who did not seroconvert to one HPV type, HPV45. This subject, with no medical history reported at baseline, also had low immune response to the other 8 HPV types with antibody titres generally much lower than the GMTs.

Although the GMTs are low, qHPV vaccine induces some level of post-dose 3 immune responses to the HPV types not included in the vaccine, including a seroconversion rate of 73.5% for HPV31, 54.8% for HPV58, 21.0% for HPV45, 20.4% for HPV33, and 3.3% for HPV52.

Table 39. Summary of Post-Dose 3 Anti-HPV Types 31, 33, 45, 52 and 58 GMTs by Vaccination Group - HPV Specific Per Protocol Set

	9vHPV Vaccine (N=300)			qHPV Vaccine (N=300)		
Assay (cLIA)	n	GMT (mMU/mL)	[95% CI]	n	GMT (mMU/mL)	[95% CI]
Anti-HPV 31	276	1770.4	[1585.7;1976.6]	268	22.2	[18.9;26.1]
Anti-HPV 33	275	937.1	[845.3;1038.9]	269	4.0	[3.6;4.5]
Anti-HPV 45	275	622.4	[545.4;710.2]	271	3.2	[2.8;3.6]
Anti-HPV 52	276	927.3	[837.5;1026.9]	269	1.9	[1.8;2.1]
Anti-HPV 58	267	1348.8	[1218.3;1493.2]	261	9.4	[8.1;10.9]

cLIA=Competitive Luminex ImmunoAssay; CI=Confidence Interval; GMT=Geometric Mean Titer; mMU=Milli Merck units

Overall, the results from the 9vHPV group in study 009/GDS01C are well in agreement with the results from the corresponding group in study 002.

Study 003

During the procedure for MAA, the Applicant has submitted preliminary results and then the final clinical study report for study 003. The study design, methods and main results are briefly described.

Study title

A Phase III Clinical Trial to Study the Tolerability and Immunogenicity of V503, a Multivalent Human Papillomavirus (HPV) L1 Virus-Like Particle (VLP) Vaccine, in 16- to 26-Year-Old Men and 16- to 26-Year-Old Women

Objectives

Primary Objective 1: To evaluate the tolerability of the 9-valent HPV L1 VLP vaccine in young men and women 16 to 26 years of age.

Primary Objective 2: To demonstrate that administration of the 9-valent HPV L1 VLP vaccine induces non-inferior Geometric Mean Titres (GMTs) for serum anti-HPV 6, anti-HPV 11, anti-HPV 16, anti-HPV 18, anti-HPV 31, anti-HPV 33, anti-HPV 45, anti-HPV 52, and anti-HPV 58 in young heterosexual men 16 to 26 years of age compared to young women 16 to 26 years of age.

Secondary objective 1: To demonstrate that the 9-valent HPV L1 VLP vaccine induces non-inferior antibody responses with respect to seroconversion percentages to HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 in young heterosexual men 16 to 26 years of age compared to young women 16 to 26 years of age.

Secondary objective 2: To evaluate serum anti-HPV 6, anti-HPV 11, anti-HPV 16, anti-HPV 18, anti-HPV 31, anti-HPV 33, anti-HPV 45, anti-HPV 52, and anti-HPV 58 antibody responses at 4 weeks post-dose 3 in MSM subjects.

Treatment

All subjects received the same formulation of 9vHPV vaccine. Study vaccine was administered as a 0.5-mL intramuscular injection at Day 1, Month 2 and Month 6. The deltoid muscle of the non-dominant arm was the preferred site of vaccination.

Treatment groups

16-26 year-old males (HM)	1,106 Subjects Randomized
16-26 year-old males (MSM)	313 Subjects Randomized
16-26 year-old females	1,101 Subjects Randomized

Endpoints

The primary immunogenicity endpoints for evaluating antibody response to 9vHPV vaccine are geometric mean titres (GMTs) to HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 at Week 4 Post-dose 3.

The secondary endpoints for evaluating antibody response to 9-valent HPV L1 VLP are the percentages of subjects who seroconvert for each HPV type (6, 11, 16, 18, 31, 33, 45, 52, and 58) by Week 4 Post-dose 3. (Seroconversion is defined as changing serostatus from seronegative at baseline to seropositive by Week 4 Post-dose 3. A subject with a cLIA titre at or above the serostatus cut-off for a given HPV type is considered seropositive for that type.)

Immunogenicity Results

Disposition of Subjects (All Randomized Subjects) (Day 1 to Month 12):

	16-26-year old males (HM)		16-26-year old males (MSM)		16-26-year old females		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	1,106		313		1,101		2,520	
Vaccinated at								
Vaccination 1	1,103	(99.7)	313	(100.0)	1,099	(99.8)	2,515	(99.8)
Vaccination 2	1,089	(98.5)	298	(95.2)	1,069	(97.1)	2,456	(97.5)
Vaccination 3	1,067	(96.5)	291	(93.0)	1,037	(94.2)	2,395	(95.0)
Trial Disposition								
Completed	1,053	(95.2)	282	(90.1)	1,015	(92.2)	2,350	(93.3)
Discontinued	49	(4.4)	31	(9.9)	82	(7.4)	162	(6.4)
Adverse Event	0	(0.0)	1	(0.3)	2	(0.2)	3	(0.1)
Lost To Follow-Up	30	(2.7)	20	(6.4)	56	(5.1)	106	(4.2)
Physician Decision	0	(0.0)	0	(0.0)	2	(0.2)	2	(0.1)
Protocol Violation	0	(0.0)	1	(0.3)	2	(0.2)	3	(0.1)
Screen Failure	2	(0.2)	0	(0.0)	2	(0.2)	4	(0.2)
Withdrawal By Subject	17	(1.5)	9	(2.9)	18	(1.6)	44	(1.7)
Unknown	4	(0.4)	0	(0.0)	4	(0.4)	8	(0.3)
Subject Study Medication Disposition								
Completed	1,067	(96.5)	291	(93.0)	1,037	(94.2)	2,395	(95.0)
Discontinued	37	(3.3)	22	(7.0)	62	(5.6)	121	(4.8)
Adverse Event	1	(0.1)	1	(0.3)	3	(0.3)	5	(0.2)
Lost To Follow-Up	21	(1.9)	11	(3.5)	39	(3.5)	71	(2.8)
Physician Decision	0	(0.0)	0	(0.0)	2	(0.2)	2	(0.1)
Protocol Violation	0	(0.0)	1	(0.3)	2	(0.2)	3	(0.1)
Withdrawal By Subject	15	(1.4)	9	(2.9)	16	(1.5)	40	(1.6)
Unknown	2	(0.2)	0	(0.0)	2	(0.2)	4	(0.2)

Each subject is counted once for Trial Disposition, Subject Study Medication Disposition based on the latest corresponding disposition record.
Unknown: A disposition record did not exist at the time of reporting.
HM = Heterosexual men, MSM = Men having sex with men.

Immunological Bridging from the Primary Efficacy Population (Females 16 to 26 Years of Age to Males 16 to 26 Years of Age)

Administration of 9vHPV vaccine to heterosexual males (HM) 16 to 26 years of age seronegative at baseline for 9vHPV vaccine types results in anti-HPV (vaccine types) antibody responses (GMTs) at 4 weeks post- dose 3 that are 1.09- to 1.25-fold higher than those observed among females 16 to 26 years of age seronegative at baseline for 9vHPV vaccine types. The statistical criterion for non-inferiority with respect to GMT required that the lower bound of the 95% CI for the fold-difference in anti-HPV 6, anti-HPV 11, anti-HPV 16, anti-HPV 18, anti-HPV 31, anti-HPV 33, anti-HPV 45, anti-HPV 52, and anti-HPV 58 GMTs (males vs. females) be above 0.67. These results are displayed in Table 39.

Table 40. Non-Inferior Month 7 HPV cLIA Geometric Mean Titres in Males 16 to 26 Years of Age Who Received 9vHPV Vaccine vs. Females 16 to 26 Years of Age Who Received 9vHPV Vaccine (Per-Protocol Immunogenicity Population) (Protocol V503-003)

	Males 16 to 26 Years of Age (N = 1,103)		**Females 16 to 26 Years of Age (N = 1,099)**		**Males 16 to 26/ Females 16 to 26**	
Assay	**n**	**GMT mMU/mL**	**n**	**GMT mMU/mL**	**GMT Ratio**	**95% CI***
Anti-HPV 6	847	782.0	708	703.9	1.11	(1.02, 1.21)
Anti-HPV 11	851	616.7	712	564.9	1.09	(1.00, 1.19)
Anti-HPV 16	899	3346.0	781	2788.3	1.20	(1.10, 1.30)
Anti-HPV 18	906	808.2	831	679.8	1.19	(1.08, 1.31)
Anti-HPV 31	908	708.5	826	570.1	1.24	(1.13, 1.37)
Anti-HPV 33	901	384.8	853	322.0	1.19	(1.10, 1.30)
Anti-HPV 45	909	235.6	871	185.7	1.27	(1.14, 1.41)
Anti-HPV 52	907	386.8	849	335.2	1.15	(1.05, 1.26)
Anti-HPV 58	897	509.8	839	409.3	1.25	(1.14, 1.36)

* p-value <0.001

N = Number of individuals randomized to the respective vaccination group who received at least one vaccination
n = Number of individuals contributing to the analysis
GMT = Geometric mean titre; mMU = milli-Merck units; CI = Confidence interval; HPV = Human papillomavirus

Immunogenicity Assessment in Men-Having-Sex-With-Men (MSM)

Administration of 9vHPV vaccine to baseline 9vHPV vaccine type-naïve MSM 16 to 26 years of age results in anti-HPV 6, anti-HPV 11, anti-HPV 16, anti-HPV 18, anti-HPV 31, anti-HPV 33, anti- HPV 45, anti-HPV 52, and anti-HPV 58 antibody responses (GMTs) at 4 weeks post- dose 3 that are numerically lower than those for HM. These results are consistent with those seen in prior studies of qHPV vaccine. Seroconversion rates at Month 7 in both MSM and HM are >99%.

Table 41. Month 7 HPV cLIA Geometric Mean Titres in HM and MSM Who Received 9vHPV Vaccine (Per-Protocol Immunogenicity Population) (Protocol V503-003)

	HM 16 to 26 Years of Age (N = 1,103)			**MSM 16 to 26 Years of Age (N = 313)**		
Assay	**n**	**GMT mMU/mL**	**95% CI**	**n**	**GMT mMU/mL**	**95% CI**
Anti-HPV 6	847	782.0	(738.0, 828.7)	164	568.9	(498.7, 649.0)
Anti-HPV 11	851	616.7	(582.4, 653.0)	165	437.7	(384.4, 498.5)
Anti-HPV 16	899	3346.0	(3158.9, 3544.1)	212	2294.0	(2037.8, 2582.5)
Anti-HPV 18	906	808.2	(754.9, 865.4)	220	608.1	(529.4, 698.5)
Anti-HPV 31	908	708.5	(662.7, 757.6)	227	420.7	(368.0, 480.9)
Anti-HPV 33	901	384.8	(362.5, 408.4)	230	252.3	(224.2, 283.8)
Anti-HPV 45	909	235.6	(219.0, 253.6)	232	157.5	(136.2, 182.2)
Anti-HPV 52	907	386.8	(363.4, 411.6)	232	233.1	(206.0, 263.7)
Anti-HPV 58	897	509.8	(479.9, 541.6)	223	319.8	(283.2, 361.0)

N = Number of individuals randomized to the respective vaccination group who received at least one vaccination
n = Number of individuals contributing to the analysis
GMT = Geometric mean titre; mMU = milli-Merck units; CI = Confidence interval; HPV = Human papillomavirus

The immunogenicity results do not indicate any differences in antibody responses that could indicate differences in efficacy for clinical endpoints relevant to males. The results are overall in agreement with the expected outcome based on the experience with qHPV.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 42. Summary of Efficacy for trial 001 (Part B)

Title: Randomized, International, Double-Blinded (With In-House Blinding), Controlled With GARDASIL™, Dose-Ranging, Tolerability, Immunogenicity, and Efficacy Study of a Multivalent Human Papillomavirus (HPV) L1 Virus-Like Particle (VLP) Vaccine Administered to 16- to 26-Year-Old Women			
Study identifier	001		
Design	Randomized, double-blind (operating under in-house blinding procedures), controlled with qHPV vaccine, multicenter, multinational, dose-ranging, safety, immunogenicity and efficacy study		
	Duration of main phase: Duration of Extension phase:	Subjects received 9vHPV vaccine or qHPV vaccine at Day 1, Month 2, and Month 6. All subjects were followed for safety Day 1 through Month 7. Subjects were assessed for immunogenicity at Month 7. ongoing	
Hypothesis	Part A: dose finding Part B: Non-inferiority of 9vHPV compared to qHPV in women 16-26 years old		
Treatments groups Part B	All subjects received 3 doses of the respective dose: Mid-dose 9vHPV: 30/40/60/40/20/20/20/20/20 µg HPV 6/11/16/18/31/33/45/52/58 VLP with 500 µg aluminum adjuvant/0.5 mL (n=7106) qHPV: 20/40/40/20 ug HPV 6/11/16/18 VLP with 225 ug aluminum adjuvant/0.5 mL (n=7109)		
Endpoints and definitions	Primary efficacy endpoint	Combined incidence of HPV 31-, 33-, 45-, 52-, and 58-related high-grade cervical abnormalities (CIN 2/3), Adenocarcinoma In Situ (AIS), invasive cervical carcinoma, high-grade Vulvar Intraepithelial Neoplasia (VIN 2/3), high-grade Vaginal Intraepithelial Neoplasia (VaIN 2/3), vulvar cancer, or vaginal cancer.	
	Immunogenicity endpoint	GMTs and seroconversion rates for HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 at 4 weeks post-dose 3	
Database lock	10 April 2013 (Clinical Study report data – median follow-up of 40 months post dose 3)		
Results and Analysis			
Analysis description	Primary Analysis		
Analysis population and time point description	Per protocol efficacy		
Descriptive statistics and estimate variability	Treatment group	9vHPV	qHPV
	Number of subjects	6016	6017
	Cases of HPV 31/33/45/52/58-Related CIN 2/3, AIS, Cervical Cancer, VIN 2/3, VaIN 2/3, Vulvar Cancer, and Vaginal Cancer	1	30

Effect estimate per comparison	Primary endpoint HPV31/33/45/52/ 58 -related CIN 2/3, AIS, Cervical Cancer, VIN 2/3, VaIN 2/3, Vulvar Cancer, and Vaginal Cancer	Comparison groups	9vHPV and qHPV
		Observed efficacy (point estimate vs. qHPV)	**96.7%**
		95% CI	80.9%; 99.8%
		P-value	<0.0001
	Secondary efficacy analysis for HPV 6/11/16/18 -related Cervical, Vulvar, and Vaginal Disease	Comparison groups	9vHPV and qHPV
		Risk reduction in incidence of endpoint compared to qHPV group	14.1%
		95% CI	-185; 71
		P-value Interpretation	N/A A 95% CI of RR that includes 0% indicates that the incidences of the endpoint in the two vaccine groups are similar, i.e. the difference is not statistically significant
	Secondary efficacy analysis for HPV16/18 related persistent infection, cervical, vulvar, vaginal disease	Comparison groups	9vHPV and qHPV
		Risk reduction in incidence of endpoint relative to historical placebo	9vHPV: **93.5**% (91.5%, 95.3%) qHPV: **89.8%** (87.0%, 92.0%) Difference: **3.8%** (0.8%, 7.2%)
		Non-inferiority criterion: lower bound of the 95% CI for the difference of efficacy (9vHPV – qHPV) should be greater than −15 % points	Fulfilled
		P-value Interpretation	N/A RR represents the efficacy of a HPV vaccine relative to an unvaccinated population. When the point estimate of RR is positive and the lower limit of the 95% CI of RR is also positive, the estimate of RR is suggestive of an incremental prophylactic protection conferred by 9vHPV vaccine in addition to the prophylactic protection conferred by qHPV vaccine

Immunogenicity results to extrapolate protection against HPV types 6-11-16-18	Primary endpoints for comparison of immune responses based on cLIA titres (GMTs at M7) between 9v-HPV vs. qHPV vaccine	Anti-HPV6 1.02 (0.99, 1.06) Anti-HPV11 0.80 (0.77, 0.83) Anti-HPV16 0.99 (0.96, 1.03) Anti-HPV18 1.19 (1.14, 1.23)	Non-inferiority for GMTs is defined as the lower bound of the two-sided 95% confidence interval for the GMT ratio of 9-valent vaccine vs. qHPV being greater than 0.67
Notes	In conclusion the 9vHPV vaccine was shown in women 16-26 years of age to: • protect against the composite clinical endpoint of HPV 31/33/45/52/58-Related CIN 2/3, AIS, Cervical Cancer, VIN 2/3, VaIN 2/3, Vulvar Cancer, and Vaginal Cancer compared to qHPV; • provide similar protection against HPV 6/11/16/18-Related Cervical, Vulvar, and Vaginal Disease compared to qHPV; • demonstrate non-inferior immune responses to HPV 6, 11, 16 and 18 for the 9vHPV vaccine compared to the qHPV vaccine in women 16-26 years.		

Table 43. Summary of Efficacy for trial 002 (immunogenicity endpoints)

Title: A Phase III Clinical Trial to Study the Immunogenicity, Tolerability, and Manufacturing Consistency of V503 (A Multivalent Human Papillomavirus [HPV] L1 Virus-Like Particle [VLP] Vaccine) in Preadolescents and Adolescents (9 to 15 year olds) with a Comparison to Young Women (16 to 26 year olds)		
Study identifier	Study 002	
Design	International, multi-centred, immunogenicity, safety, and manufacturing consistency study of the 9vHPV vaccine. Two immunogenicity substudies were conducted: an adult-adolescent immunobridging substudy, and a lot manufacturing consistency substudy.	
	Duration of main phase:	Subjects received 9vHPV vaccine or qHPV vaccine at Day 1, Month 2, and Month 6. All subjects were followed for safety Day 1 through Month 12. Subjects were assessed for immunogenicity at Month 7.
	Duration of Extension phase:	Ongoing. Follow-up planned up to month 36.

Hypothesis	Immunogenicity1: Non-inferior immune responses to all 9 HPV vaccine types in preadolescent and adolescent girls 9 to 15 years of age compared to young women 16 to 26 years of age. Immunogenicity 2: To demonstrate that the Final Manufacturing Process results in 9-valent HPV L1 VLP vaccine that induces consistent serum responses to all 9 vaccine HPV types. (data not shown in this table)			
Treatments groups	Boys and girls 9-15 years Women 16-26 years	All subjects received 3 doses of either: 9vHPV: 30/40/60/40/20/20/20/20/20 µg HPV 6/11/16/18/31/33/45/52/58 VLP with 500 µg aluminum adjuvant/0.5 mL; three different consistency lots were used. qHPV: 20/40/40/20 ug HPV 6/11/16/18 VLP with 225 ug aluminum adjuvant/0.5 mL		
Endpoints and definitions	Immunogenicity	Serum anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 titres were measured using a competitive Luminex Immunoassay (HPV-9 cLIA). The following endpoints were collected from each study subject to assess immunogenicity: 1) cLIA titres for each of the vaccine HPV types; 2) seroconversion status (i.e., above or below serostatus cutoff) for each of the vaccine HPV types.		
Database lock	August 18, 2011			
Results and Analysis				
Analysis description	Primary Analysis			
Analysis population and time point description	Per protocol Immunogenicity population Primary time point: month 7			
Descriptive statistics and estimate variability	Treatment group	9-15 year old females	9-15 year old males	16-26 year old females
	Number of subject	646	666	468
	Anti HPV 6 GMT	**1,715**	**2,085**	**900.8**
	95% CI	1,595; 1,845	1,944; 2,236	822.3; 986.9
	Anti HPV 11 GMT	**1,295**	**1,487**	**706.6**
	95% CI	1,204; 1,393	1,386; 1,595	645.2, 773.8

	Anti HPV 16 GMT	**6,980**	**8,629**	**3,523**
	95% CI	6,508; 7,486	8,066; 9,231	3,224; 3,850
	Anti HPV 18 GMT	**2,154**	**2,823**	**882.7**
	95% CI	1,980; 2,342	2,603; 3,062)	795.4; 979.5
	Anti HPV 31 GMT	**1,892**	**2,221**	**753.9**
	95% CI	1,746; 2,050	2,056; 2,400	682.5; 832.7
	Anti HPV 33 GMT	**980.4**	**1,199**	**466.8**
	95% CI	911.7; 1,054	1,117; 1,286	426.9; 510.3
	Anti HPV 45 GMT	**714.4**	**907.0**	**272.2**
	95% CI	651.9; 782.8	830.2; 991.0	243.8; 303.9
	Anti HPV 52 GMT	**932.9**	**1,038**	**419.6**
	95% CI	864.8; 1,006	964.4; 1,117	381.4, 461.5
	Anti HPV 58 GMT	**1,287**	**1,568**	**590.5**
	95% CI	1,196; 1,385	1,460; 1,683	538.2, 647.9

Effect estimate per comparison	Primary endpoint	Comparison groups	9- to 15-Year-Old Females 16- to 26-Year-Old Females
	HPV 6	Fold Difference of GMT	**1.90**
		95% CI	1.70; 2.14
		P-value	<0.001
	HPV 11	Fold Difference of GMT	**1.83**
		95% CI	1.63; 2.06
		P-value	<0.001
	HPV 16	Fold Difference of GMT	**1.98**
		95% CI	1.77; 2.22
		P-value	<0.001
	HPV 18	Fold Difference of GMT	**2.44**
		95% CI	2.13; 2.80
		P-value	<0.001
	HPV 31	Fold Difference of GMT	**2.51**

		95% CI	2.21; 2.85
		P-value	<0.001
	HPV 33	Fold Difference of GMT	**2.10**
		95% CI	1.87; 2.36
		P-value	<0.001
	HPV 45	Fold Difference of GMT	**2.62**
		95% CI	2.27; 3.03
		P-value	<0.001
	HPV 52	Fold Difference of GMT	**2.22**
		95% CI	1.97; 2.51
		P-value	<0.001
	HPV 58	Fold Difference of GMT	**2.18**
		95% CI	1.93; 2.45
		P-value	<0.001
Notes	In conclusion, non-inferior antibody responses to all HPV types were demonstrated in 9-15 year olds compared to 16-26 year olds (i.e. the population in which efficacy was established). In addition, manufacturing lot consistency was demonstrated for the three consistency lots (data not included in this table)		

Table 44. Summary of Efficacy for trial 009/GDS01C (immunogenicity endpoints)

Title: A Randomized, Double-Blinded, Controlled with GARDASIL (Human Papillomavirus Vaccine [Types 6, 11, 16, 18] (Recombinant, adsorbed)), Phase III Clinical Trial to Study the Immunogenicity and Tolerability of V503 (9-Valent Human Papillomavirus [HPV] L1 Virus-Like Particle [VLP] Vaccine) in Preadolescent and Adolescent Girls (9- to 15-year-olds)		
Study identifier	009 / GDS01C	
Design	European, multi-centre, double-blinded, randomized, controlled with qHPV vaccine, immunogenicity and tolerability study of the 9-valent HPV L1 VLP vaccine in preadolescent and adolescent girls (9 to 15 years of age)	
	Duration of main phase:	Subjects received 9vHPV vaccine or qHPV vaccine at Day 1, Month 2, and Month 6. All subjects were followed for safety Day 1 through Month 7. Subjects were assessed for immunogenicity at Month 7.
	Duration of Extension phase:	None.
Hypothesis	Non-inferiority of immune responses to 9vHPV compared to QHPV in 9-15 year old girls	

Treatments groups	9vHPV	All subjects received 3 doses of: 30/40/60/40/20/20/20/20/20 µg HPV 6/11/16/18/31/33/45/52/58 VLP with 500 µg aluminum adjuvant/0.5 mL
	qHPV	All subjects received 3 doses of: 20/40/40/20 ug HPV 6/11/16/18 VLP with 225 ug aluminum adjuvant/0.5 mL
Endpoints and definitions	Primary endpoint: Immunogenicity	Serum anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 titres were measured using a competitive Luminex Immunoassay (HPV-9 cLIA). The following endpoints were collected from each study subject to assess immunogenicity: 1) cLIA titres for each of the vaccine HPV types; 2) seroconversion status (i.e., above or below serostatus cutoff) for each of the vaccine HPV types.

Results and Analysis

Analysis description	Primary Analysis		
Analysis population and time point description	Per protocol immunogenicity population. Month 7.		
Descriptive statistics and estimate variability	Treatment group	9vHPV vaccine	qHPV vaccine
	Number of subjects	276	271
	Anti HPV 6 GMT	**1679**	**1566**
	95% CI	1519; 1857	1412; 1736
	Anti HPV 11 GMT	**1316**	**1417**
	95% CI	1184; 1462	1274; 1576
	Anti HPV 16 GMT	**6740**	**6887**
	95% CI	1737; 2204	1567; 2057

	Anti HPV 18 GMT	**1957**	**1796**
	95% CI	1737; 2204	1567; 2057
Effect estimate per comparison	Primary endpoint	Comparison groups	9vHPV vaccine qHPV vaccine
	HPV 6	Estimated GMT ratio 9vHPV / qHPV	**1.07**
		95% CI	0.93; 1.23
		P-value	<0.001
	HPV 11	Estimated GMT ratio 9vHPV / qHPV	**0.93**
		95% CI	0.80; 1.08
		P-value	<0.001
	HPV 16	Estimated GMT ratio 9vHPV / qHPV	**0.97**
		95% CI	0.85;1.11
		P-value	<0.001
	HPV 18	Estimated GMT ratio 9vHPV / qHPV	**1.08**
		95% CI	0.91; 1.29
		P-value	<0.001
Notes	In conclusion, the immune responses to HPV 6, 11, 16 and 18 after vaccination with 9vHPV vaccine were found to be non-inferior to the responses to qHPV vaccine in girls 9-15 years of age.		

Table 45. Summary of Efficacy for trial 003 (immunogenicity endpoints)

Title: A Phase III Clinical Trial to Study the Tolerability and Immunogenicity of V503, a Multivalent Human Papillomavirus (HPV) L1 Virus-Like Particle (VLP) Vaccine, in 16- to 26-Year-Old Men and 16- to 26-Year-Old Women	
Study identifier	003
Design	This was a Phase III, open-label, international, multicenter, clinical study to evaluate the immunogenicity and tolerability of the 9-valent HPV L1 VLP (9vHPV) vaccine in healthy young HM men (16 to 26 years of age) in comparison to healthy young women (16 to 26 years of age).

	Duration of main phase: Duration of Extension phase:	Subjects received 9vHPV vaccine or qHPV vaccine at Day 1, Month 2, and Month 6. All subjects were followed for safety Day 1 through Month 12. Subjects were assessed for immunogenicity at Month 7. None.		
Hypothesis	Non-inferior immune responses to all 9 HPV vaccine types in males 16-26 years of age compared to young women 16 to 26 years of age.			
Treatments groups	9vHPV	All subjects received 3 doses of: 30/40/60/40/20/20/20/20/20 µg HPV 6/11/16/18/31/33/45/52/58 VLP with 500 µg aluminum adjuvant/0.5 mL		
Endpoints and definitions	Primary endpoint: Immunogenicity	Serum anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 titres were measured using a competitive Luminex Immunoassay (HPV-9 cLIA). The following endpoints were collected from each study subject to assess immunogenicity: 1) cLIA titres for each of the vaccine HPV types; 2) seroconversion status (i.e., above or below serostatus cutoff) for each of the vaccine HPV types.		
Results and Analysis				
Analysis description	Primary Analysis			
Analysis population and time point description	Per protocol immunogenicity population. Month 7.			
Descriptive statistics and estimate variability	Treatment group	16-26 year old males (HM)	16-26 year old males (MSM	16-26 year old females
	Number of subjects	1103	313	1099
	Anti HPV 6 GMT	782.0	568.9	703.9
	95% CI	738.0, 828.7	498.7, 649.0	660.6; 749.9
	Anti HPV 11 GMT	616.7	437.7	564.9
	95% CI	582.4, 653.0	384.4, 498.5	530.6; 601.3
	Anti HPV 16 GMT	3346.0	2294.0	2788.3

	95% CI	3158.9, 3544.1	2037.8, 2582.5	2621.4; 2965.8
	Anti HPV 18 GMT 95% CI	808.2 754.9, 865.4	608.1 529.4, 698.5	679.8 633.1; 730.1
	Anti HPV 31 GMT 95% CI	708.5 662.7, 757.6	420.7 368.0, 480.9	570.1 531.5; 611.5
	Anti HPV 33 GMT 95% CI	384.8 362.5, 408.4	252.3 224.2, 283.8	322.0 302.9; 342.3
	Anti HPV 45 GMT 95% CI	235.6 219.0, 253.6	157.5 136.2, 182.2	185.7 172.3, 200.2
	Anti HPV 52 GMT 95% CI	386.8 363.4, 411.6	233.1 206.0, 263.7	335.2 314.3; 357.6
	Anti HPV 58 GMT 95% CI	509.8 479.9, 541.6	319.8 283.2, 361.0	409,3 384.5; 435.7
Effect estimate per comparison	Primary endpoint	Estimated GMT ratio (95% CI) 16-26 year old males/16-26 year old females		
	HPV 6	1.11 (1.02; 1.21)		
	HPV 11	1.09 (1.02, 1.21)		
	HPV 16	1.20 (1.10, 1.30)		
	HPV 18	1.19 (1.08, 1.31)		
	HPV 31	1.24 (1.13, 1.37)		
	HPV 33	1.19 (1.10, 1.30)		
	HPV 45	1.27 (1.14, 1.41)		
	HPV52	1.15 (1.05, 1.26)		
	HPV58	1.25 (1.14, 1.36)		

Notes	In conclusion, anti-HPV vaccine types GMTs and seroconversion rates at 4 weeks post-dose 3 in heterosexual men (HM) were non-inferior to those observed in 16- to 26-year-old women.

Analysis performed across trials

Immunogenicity of 9vHPV vaccine in subjects not previously vaccinated with HPV vaccine was analysed across study protocols in the PPI population by age and gender (measured by GMTs and by percentage of individuals who were seropositive against the relevant vaccine HPV type):

- For females 16-26 years of age (studies P001 and P002), the overall Month 7 cLIA GMTs were 893.7 for HPV 6, 669.3 for HPV-11, 3,159.0 for HPV 16, 809.9 for HPV 18, 664.8 for HPV 31, 419.2 for HPV 33, 254.1 for HPV 45, 382.4 for HPV 52, and 489.2 for HPV 58. The overall Month 7 seroconversion rates were $\geqslant$ 99.5% for each vaccine HPV type.
- For females 9-15 years of age (studies P002, P005, P007, P009), the overall Month 7 cLIA GMTs were 1,744.6 for HPV 6, 1,289.7 for HPV-11, 7,159.9 for HPV 16, 2,085.5 for HPV 18, 1,883.3 for HPV 31, 960.6 for HPV 33, 728.7 for HPV 45, 978.2 for HPV 52, and 1,306.0 for HPV 58. The overall Month 7 seroconversion rates were $\geqslant$ 99.6% for each vaccine HPV type.
- For males 9-15 years of age (studies P002, P005, P007), the overall Month 7 cLIA GMTs were 2,085.3 for HPV 6, 1,469.2 for HPV-11, 8,444.9 for HPV 16, 2,620.4 for HPV 18, 2,173.5 for HPV 31, 1,178.6 for HPV 33, 841.7 for HPV 45, 1,062.2 for HPV 52, and 1,545.8 for HPV 58. The overall Month 7 seroconversion rates were $\geqslant$ 99.8% for each vaccine HPV type.

Supportive studies

Studies 005, 006, and 007 are summarised in this section. Study 005 and 007 investigate concomitant vaccinations and study 006 investigate the effects of 9vHPV in prior qHPV recipients.

Study 005

This study was an open-label, randomized, multicentre, comparative study to evaluate the tolerability and immunogenicity of the concomitant administration of the first dose of the 9vHPV vaccine with Menactra and Adacel versus the non-concomitant administration of the 9vHPV vaccine with Menactra and Adacel. A total of 1254 subjects were screened for inclusion in this study; 1241 were randomized (621 in the Concomitant Group and 620 in the Non-concomitant Group) and 1,237 received vaccination.

GMTs for each vaccine HPV type of the 9vHPV vaccine were measured at 4 weeks post-dose 3 (Month 7). Table 45 presents the results of the PP analysis, which showed non-inferiority of anti-HPV responses in the group that received concomitant injections compared with the group that received non-concomitant injections (i.e. Menactra and Adacel were given one month after 9vHPV).

Table 46. Statistical Analysis of Non-Inferiority Comparing Month 7 HPV cLIA Geometric Mean Titres (HPV-types 6, 11, 16, 18, 31, 33, 45, 52 and 58) Between Concomitant vs. Non-concomitant Vaccination Group (Per-Protocol Immunogenicity Population - HPV)

	9vHPV Vaccine + [Menactra™ + Adacel™] (Concomitant) (Comparison Group A) (N = 619)		9vHPV Vaccine + [Menactra™ + Adacel™] (Non-concomitant) (Comparison Group B) (N = 618)		Estimated Fold Difference Group A / Group B	p-Value for
Assay (cLIA)	n	Estimated GMT (mMU/mL)	n	Estimated GMT (mMU/mL)	(95% CI)	Non-Inferiority‡
Anti-HPV 6	501	2,198.7	514	2,260.7	0.97 (0.88, 1.08)	<0.001
Anti-HPV 11	502	1,495.0	514	1,547.2	0.97 (0.87, 1.07)	<0.001
Anti-HPV 16	513	8,882.6	530	9,027.6	0.98 (0.89, 1.09)	<0.001
Anti-HPV 18	516	2,610.4	535	2,633.9	0.99 (0.88, 1.12)	<0.001
Anti-HPV 31	514	2,439.4	536	2,334.3	1.04 (0.93, 1.17)	<0.001
Anti-HPV 33	520	1,268.5	537	1,276.3	0.99 (0.89, 1.11)	<0.001
Anti-HPV 45	523	947.8	539	863.8	1.10 (0.97, 1.25)	<0.001
Anti-HPV 52	521	1,082.7	538	1,103.7	0.98 (0.88, 1.10)	<0.001
Anti-HPV 58	519	1,532.8	537	1,555.1	0.99 (0.88, 1.10)	<0.001
Overall conclusion: The non-inferiority criterion was met for all 9 HPV types.						

‡The noninferiority criterion for endpoints reported in this table is defined as statistically less than a 2-fold decrease in Group A compared to Group B. Noninferiority of GMT in Group A relative to Group B is demonstrated if the lower limit of the 95% CI for the fold difference is greater than 0.5.
The estimated GMT, fold difference, associated confidence intervals, and p-values are based on a statistical analysis model.
N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects contributing to the analysis.
CI = Confidence interval; GMT = Geometric mean titre; mMU = Milli Merck units; cLIA = Competitive Luminex immunoassay; 9vHPV = Nine-Valent Human Papillomavirus (Types 6, 11, 16, 18, 31, 33, 45, 52, 58) Recombinant Vaccine.

In addition, serological non-inferiority was also demonstrated for Menactra and Adacel between the 2 treatment groups.

Study 007

This study was an open-label, randomized, multicentre, comparative study to evaluate the tolerability and immunogenicity of the concomitant administration of the first dose of the 9vHPV vaccine with Repevax versus the non-concomitant administration of 9vHPV vaccine with Repevax. A total of 1,074 subjects were screened for inclusion in this study and 1,054 were randomized (526 in the Concomitant Group and 528 in the Non-concomitant Group) and 1,053 received vaccination.

GMTs for each vaccine HPV type of the 9vHPV vaccine were measured 4 weeks post-dose 3 (Month 7). Table 46 presents the results of the PP analysis, which showed non-inferiority of anti-HPV responses in the group that

received the 9vHPV vaccine and Repevax injections concomitant vs. the group that received non-concomitant 9vHPV vaccine and Repevax injections.

Table 47. Statistical Analysis of Non-Inferiority Comparing Month 7 HPV cLIA Geometric Mean Titres (HPV-types 6, 11, 16, 18, 31, 33, 45, 52 and 58) Between Concomitant vs. Non-concomitant Vaccination Group (Per-Protocol Immunogenicity Population - HPV)

	9vHPV Vaccine + Repevax™ (Concomitant) (Comparison Group A) (N = 525)		9vHPV Vaccine + Repevax™ (Non-concomitant) (Comparison Group B) (N = 528)		Estimated Fold Difference	
Assay (cLIA)	n	Estimated GMT (mMU/mL)	n	Estimated GMT (mMU/mL)	Group A / Group B (95% CI)	p-Value for Non-Inferiority‡
Anti-HPV 6	477	1,637.9	461	1,725.0	0.95 (0.86, 1.05)	<0.001
Anti-HPV 11	479	1,170.3	462	1,212.6	0.97 (0.87, 1.07)	<0.001
Anti-HPV 16	489	6,529.4	479	6,940.6	0.94 (0.85, 1.04)	<0.001
Anti-HPV 18	486	1,854.1	475	1,954.8	0.95 (0.84, 1.07)	<0.001
Anti-HPV 31	485	1,646.2	473	1,750.6	0.94 (0.84, 1.06)	<0.001
Anti-HPV 33	487	823.8	478	915.5	0.90 (0.81, 1.00)	<0.001
Anti-HPV 45	489	658.2	478	675.6	0.97 (0.86, 1.11)	<0.001
Anti-HPV 52	490	965.4	479	1,015.3	0.95 (0.85, 1.06)	<0.001
Anti-HPV 58	484	1,188.8	469	1,334.8	0.89 (0.80, 0.99)	<0.001
Overall conclusion: The non-inferiority criterion was met for all 9 HPV types.						

‡The noninferiority criterion for endpoints reported in this table is defined as statistically less than a 2-fold decrease in Group A compared to Group B. Noninferiority of GMT in Group A relative to Group B is demonstrated if the lower limit of the 95% CI for the fold difference is greater than 0.5.
The estimated GMT, fold difference, associated confidence intervals, and p-values are based on a statistical analysis model.
N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects contributing to the analysis.
CI = Confidence interval; GMT = Geometric mean titre; mMU = Milli Merck units; cLIA = Competitive Luminex immunoassay; 9vHPV = Nine-Valent Human Papillomavirus (Types 6, 11, 16, 18, 31, 33, 45, 52, 58) Recombinant Vaccine.

In addition, serological non-inferiority between the 2 treatment groups was also demonstrated for Repevax.

Study 006

This study was a randomized, double-blinded, placebo-controlled, international, multi-centre study investigating safety/tolerability and immunogenicity of the 9vHPV vaccine in females 12 to 26 years of age who were previously vaccinated with qHPV. A total of 935 subjects were screened for inclusion in this study, of which 921 were randomized to have 615 subjects in the 9vHPV vaccine group and 306 subjects in the placebo group.

Table 47 presents a summary by vaccination group of the GMTs and associated 95% CIs for the immune responses to HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 at Day 1, Month 2, and Month 7. The GMTs for the 4 common HPV types were as expected very high. However, the GMTs for the 5 new HPV types were considerably lower in this study compared to the other studies. Thus, some interference of the immune responses to the new vaccine types included in 9vHPV could be hypothesised as a cause, when qHPV is given previously.

Table 48. Summary of Anti-HPV cLIA Geometric Mean titres by Vaccination Group (Modified Per-Protocol Immunogenicity Population†)

		9vHPV vaccine (N=615)			Placebo (N=306)		
Assay (cLIA)	Time Point	n	GMT (mMU/mL)	95% CI	n	GMT (mMU/mL)	95% CI
Anti-HPV 6	Day 1	499	348.2	(320.2, 378.8)	248	372.4	(330.6, 419.6)
	Month 02	505	2,426.7	(2,254.2, 2,612.3)	245	363.4	(326.9, 404.0)
	Month 07	511	2,207.4	(2,052.7, 2,373.9)	251	323.8	(291.9, 359.2)
Anti-HPV 11	Day 1	513	253.0	(232.3, 275.6)	261	263.6	(233.8, 297.1)
	Month 02	511	2,077.8	(1,925.9, 2,241.6)	256	253.3	(227.6, 282.0)
	Month 07	515	1,824.0	(1,695.5, 1,962.2)	261	225.4	(203.4, 249.7)
Anti-HPV 16	Day 1	513	1,066.1	(973.8, 1,167.1)	261	1,103.7	(972.2, 1,253.1)
	Month 02	511	13,877.6	(12,846.3, 14,991.7	256	1,076.1	(964.9, 1,200.1)
	Month 07	515	11,192.8	(10,393.6, 12,053.6	261	966.9	(871.3, 1,072.9)
Anti-HPV 18	Day 1	513	154.2	(135.4, 175.5)	261	136.1	(113.4, 163.2)
	Month 02	511	2,187.9	(1,975.2, 2,423.5)	256	130.1	(112.6, 150.3)
	Month 07	515	2,285.8	(2,067.4, 2,527.3)	261	112.8	(98.0, 129.9)
Anti-HPV 31	Day 1	513	4.1	(<4, 4.5)	261	4.3	(<4, 5.0)
	Month 02	511	201.1	(180.5, 224.0)	256	4.3	(<4, 5.0)
	Month 07	515	260.0	(237.6, 284.5)	261	4.7	(4.1, 5.3)
Anti-HPV 33	Day 1	513	< 4	(<4, <4)	261	< 4	(<4, <4)
	Month 02	511	70.0	(63.2, 77.4)	256	< 4	(<4, <4)
	Month 07	515	175.2	(162.5, 188.9)	261	< 4	(<4, <4)
Anti-HPV 45	Day 1	513	< 3	(<3, <3)	261	< 3	(<3, <3)
	Month 02	511	15.1	(13.5, 16.8)	256	< 3	(<3, <3)
	Month 07	515	97.4	(89.8, 105.7)	261	< 3	(<3, <3)
Anti-HPV 52	Day 1	513	< 3	(<3, <3)	261	< 3	(<3, <3)
	Month 02	511	56.0	(51.2, 61.2)	256	< 3	(<3, <3)
	Month 07	515	264.1	(244.6, 285.1)	261	< 3	(<3, <3)
Anti-HPV 58	Day 1	513	< 4	(<4, <4)	261	< 4	(<4, <4)
	Month 02	511	83.2	(76.4, 90.5)	256	< 4	(<4, <4)
	Month 07	515	269.7	(250.8, 290.0)	261	< 4	(<4, <4)

†The modified per-protocol immunogenicity population includes all subjects who were not general protocol violators, received all 3 vaccinations within acceptable day ranges, and had a Month 7 serum sample collected within an acceptable day range.

N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.

n = Number of subjects contributing to the analysis.

CI = Confidence interval; cLIA = Competitive Luminex immunoassay; GMT = Geometric mean titer; mMU = Milli Merck units.

In addition, seropositivity to HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58 in the per protocol population ranged from 98.3 to 100% by Month 7 in individuals who received 9vHPV vaccine.

2.2.7. Discussion on clinical efficacy

Design and conduct of clinical studies

Four main studies were assessed in the context of this application:

- 001: dose-ranging, efficacy and immunogenicity of 9vHPV and qHVP vaccines in women 16-26 years;
- 002: immunobridging study from adolescents 9-15 years to women 16-26 years receiving 9vHPV vaccine;
- 003: immunobridging study from males 16-26 years to women 16-26 years receiving 9vHPV vaccine;
- 009/GDS01C: comparative study between 9vHPV and qHPV vaccines in girls 9-15 years of age;

In addition, three supportive studies were included in the application:

- 005: concomitant vaccination with Adacel and Menactra (diphtheria-tetanus-pertussis and 4-valent meningococcal conjugate);
- 007: concomitant vaccination with Repevax (diphtheria-tetanus-pertussis-polio);
- 006: safety and immunogenicity of 9vHPV vaccine in prior qHPV vaccine recipients.

In response to the Day 120 List of questions , the Applicant submitted an end-of-study report for study 001, and a statistical report for study 002-010 (extension of study 002) and some preliminary data for study 003 (a study comparing immune responses in males and females 16-26 years). The final study report for study 003 was submitted with the responses to the Day 180 List of Outstanding issues.

The overall ethics, conduct and design of the studies was satisfactory. Efficacy and immunogenicity of the vaccine were studied in the most important target populations for vaccination (9 to 26 year-olds) and the European population was well represented. Five out of 7 studies were conducted in multiple continents ensuring sufficient diversity of the population investigated. All studies were adequately sized, relevant primary endpoints and appropriate follow-up periods were chosen to address efficacy and immunogenicity objectives. Dropout rates in each study were low, and the objectives were achieved for all studies.

There were no major deficiencies identified either in the randomization and blinding procedures or in the statistical methods. The use of a seamless phase IIb/phase III design in study 001 was in general acceptable. However, there was a concern that pooling subjects from Part A and Part B of the study for efficacy analysis could impact on the type I error. Therefore during the evaluation the Applicant submitted the results of the analysis of the primary efficacy outcome variable restricted to subjects recruited only to part B of the study. The results of this analysis only marginally differed from the results based on the pooled study population as provided with the CSR. Thus the effect of pooling data from part A and part B of the study can be considered negligible.

The clinical development program did not include any study in women ≥ 27 years of age, representing a shortcoming of this MAA. This is reflected in section 4.2 of SmPC, as a warning note for vaccine prescribers and consumers. The major risks are that the 9vHPV vaccine may induce lower GMTs for the 5 new vaccine HPV types in this age group vs. the younger age groups; however the clinical significance of this and how long these immune responses would last for is unknown. Therefore, a plan for a post-marketing immunogenicity and safety study in women 27-45 years of age was discussed and agreed with the Applicant (see RMP section).

The potential of vaccinating with 9vHPV previous qHPV recipients was also addressed during the procedure and sections 4.2, 4.4 and 5.1 of the SmPC are accurately reflecting the data. In addition, this issue is reflected in the RMP as an important identified risk (see RMP section). Briefly, Study 006 evaluated the immunogenicity of 9vHPV in 921 girls and women (12 through 26 years of age) who had previously been vaccinated with qHPV vaccine. For subjects receiving 9vHPV after receiving 3 doses of qHPV vaccine, there was an interval of at least 12 months between completion of vaccination with qHPV vaccine and the start of vaccination with 9vHPV with a 3 dose regimen (the time interval ranged from approximately 12 to 36 months). Seropositivity to HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58 in the per protocol population ranged from 98.3 to 100% by Month 7 in individuals who received 9vHPV. The GMTs to HPV Types 6, 11, 16, 18 were higher than in the population who had not previously received qHPV vaccine in other studies whereas the GMTs to HPV Types 31, 33, 45, 52 and 58 were lower. The clinical significance of this observation is not known. There are no safety, immunogenicity or efficacy data to support interchangeability of Gardasil 9 with bivalent or quadrivalent HPV vaccines.

Efficacy data and additional analyses

The efficacy of the 9vHPV vaccine has been demonstrated either directly or indirectly through serological bridging.

Efficacy in women 16-26 years of age

Direct efficacy in this age group was demonstrated for a composite endpoint of disease related to HPV types 31, 33, 45, 52 and 58 in study 001. The composite endpoint included CIN 2/3, AIS, Cervical Cancer, VIN 2/3, VaIN 2/3, Vulvar Cancer, and Vaginal Cancer. The analysis population (PP) included subjects who were naïve at enrolment to all the HPV vaccine types and remained PCR negative through to Month 7, and who received all 3 vaccine doses and did not violate the study protocol. The majority of cases were CIN2/3, and the most common HPV type was HPV 52 (11 cases in the qHPV group, which included 6017 subjects) followed by HPV 31 and 33 (7 cases each in the qHPV group). Efficacy against the composite endpoint was satisfactorily demonstrated with a point estimate of protective efficacy of 96.7% (95% CI: 80.9; 99.8) relative to qHPV as control (see table 16), which does not include the 5 serotypes of the primary analysis. In addition, statistically significant protection was demonstrated for HPV vaccine types 31, 33 and 52 against the endpoints of disease. Protective efficacy was also demonstrated against the endpoint of lack of persistent infection at 6 and 12 months post-vaccination. For all endpoints, clinical and virological, the protective efficacy was higher in the PP population compared to the HPV naïve population. This is not unexpected based on the criteria used to define the different populations (e.g. higher number of vaccine doses received in the PP population), and similar results were also seen for qHPV. Subjects in study 001 were followed up to month 54 (over 25% of subjects completed the Month 54 visit) and high vaccine efficacy was maintained up to that time point.

There were fewer CIN3 and VaIN2/3 cases contributing to the primary efficacy analysis, whilst no cases of AIS, VIN2/3, or cancers could be detected. This is not considered an issue, because the efficacy study was not designed to generate precise efficacy estimate for important individual diseases due to feasibility regarding duration and sample size in a pre-authorisation context. On the other hand, this lack of cases positively reinforces the knowledge that the 5 new HPV types included in 9vHPV are associated with lower oncogenicity and slower disease progression than e.g. 16 or 18 types. To address this point further, the Applicant will conduct an effectiveness study in the Scandinavian countries, which will contribute to further substantiate the efficacy of 9vHPV on long term disease progression. The study is included in the RMP.

Protection against the old HPV types, i.e. HPV 6, 11, 16 and 18, already included in qHPV, was demonstrated by serological bridging based on non-inferior immune response (GMTs as primary endpoint and seroconversion as secondary) of the 9vHPV vaccine vs. qHPV in women 16-26 years of age, for which efficacy against clinical endpoints was previously demonstrated. In addition, clinical and virological outcomes were compared between the 9vHPV and qHPV groups and with historical qHPV and placebo groups in exploratory analyses. Several secondary and exploratory analyses using various clinical endpoints were conducted, either related to 5 new vaccine types, all vaccine types, or irrespective of HPV type (not shown). These results provided supportive evidence for efficacy of 9vHPV vaccine in preventing all vaccine HPV types-related disease. As mentioned above, even using all vaccine types-related endpoints, vaccine efficacy against VIN2/3, AIS, cervical, vulvar and vaginal cancers could not be established in PPE population (no cases). Also, efficacy of the 9vHPV vaccine was evaluated relative to historical placebo with respect to persistent infection, cervical, vulvar, and vaginal disease related to HPV types 6, 11, 16, and 18 for each of the PPE and HNTS populations. For these analyses, efficacy was defined as the percent reduction in the historical placebo group incidence that is observed in each vaccination group. The point estimates obtained do not indicate a negative trend in protection against any endpoint, although confidence intervals are very wide for most endpoints (see further below).

As mentioned, non-inferior immune responses in terms of cLIA (Competitive Luminex Immunoassay) GMTs were demonstrated for HPV 6, 11, 16 and 18 types in women 16-26 years old. There were only minor differences in GMTs across virus types. In support of this analysis, PBNA assay (Pseudovirion-based neutralization assay) was also used and these results were in line with the cLIA results. However, the 9vHPV vaccine induced anti-HPV 11 GMTs that were 20% lower than the qHPV vaccine at Month 7 (P001). The per protocol analyses presented in study 001 showed that for HPV type 11 the estimated GMT ratio between subjects in 9vHPV group and subjects in qHPV group was 0.80 with an associated 95% confidence interval of (0.77, 0.83) (see table 41); the criterion for non-inferiority, which required that the lower bound of the 95% confidence interval be greater than 0.67, was met. Study 001 enrolled subjects 16 to 26 years of age. Given that antibody response to the vaccine may decrease with age, additional analyses were conducted to assess whether the non-inferiority criteria was met in two age strata 16-20 and 21-26 years of age, as requested by the CHMP during the procedure (not shown). Non-inferiority could still be demonstrated in the older age stratum for HPV type 11, which is reassuring also considering that no cases of HPV 11-related disease or persistent infection was found in the per protocol efficacy population. At present, such GMTs reduction did not translate into reduced vaccine efficacy against HPV type 11. Seroconversion rates were above 99% at month 7 in adolescents 9-15 years and women 16-26 years of age (similar results were observed for the new HPV types). The long-term persistence of anti-HPV response will be further evaluated in the long term follow-up (LTFU) effectiveness study V503-021 (see below and RMP section).

The number of cases of the clinical endpoints related to HPV 6/11/16/18 in the per protocol population was low (6 cases in 7000 subjects), as expected based on the efficacy demonstrated for qHPV (7 cases in 7000 subjects). Of the 6 disease cases identified in the 9vHPV group, 4 were diagnosed as condyloma related to HPV type 6. In the qHPV group, 6 of the 7 cases were related to HPV16, and they were also co-infected with non-vaccine high-risk HPV types at the time of or before the time of being diagnosed with the HPV16-related disease. The number of cases in the HPV naïve (HN-TS) population was higher (18 cases for 9vHPV and 17 cases for qHPV), but the results were consistent with the PP population results. The results for persistent infections are also in line with the results for the primary endpoints, i.e. there are only small differences between the two vaccines groups, with the 9vHPV group showing higher incidences of persistent infections by HPV 6/11 (e.g. 13 cases at 6 months PP population) and lower incidence of persistent infection by HPV 16/18 (e.g. 46 cases at 6 months PP population) as compared to the qHPV group (7 cases and 73 cases respectively, PP population).

As already mentioned, in support of demonstration of protection against HPV 6, 11, 16 and 18 by the 9vHPV vaccine, an exploratory efficacy analysis to compare the efficacy of 9vHPV and qHPV to historical placebo control (i.e. an unvaccinated population) and historical qHPV data was made. This comparison is of interest, although there are limitations and biases in this type of analysis, which need to be taken into account. For example the incidence of disease outcomes related to HPV 16/18 in the qHPV group was higher in the current study compared to the historical qHPV group. Overall, non-inferiority of 9HPV efficacy against HPV 16/18-related persistent infection at month 6, and against cervical, vulvar, and vaginal disease compared to qHPV was satisfactorily demonstrated; however the absolute risk reductions vs. historical placebo group (9vHPV: RRh 93.5%, 95% CI (91.5%, 95.3%); qHPV: RRh 89.8%, 95% CI (87.0%, 92.0%)) should be interpreted with caution due to the inherent limitations of this type of analyses.

The lack of cross-protection against non-vaccine HPV types might result in serotype replacement when the 9vHPV vaccine will be widespread used. For qHPV, no increase in disease incidence caused by non-vaccine HPV types occurred up to at least 6 years post-dose 3. However, it remains unknown whether the 9vHPV vaccine will behave similarly, but this will be monitored in long-term follow-up studies.

Efficacy in boys and girls 9-15 years of age

As for qHPV, protection cannot be demonstrated in a 9-15 year old population due to sexual naivety. Therefore, serological bridging to the efficacy population has been accepted as a surrogate for demonstration of protection in this target population. Non-inferior immune responses were demonstrated between girls and boys 9-15 years of age compared to women 16-26 years of age, in which vaccine efficacy was demonstrated with clinical disease endpoints. In addition, non-inferiority of GMTs to HPV types 6, 11, 16 and 18 in girls 9-15 years of age receiving 9vHPV compared to the same population receiving the qHPV was also demonstrated. Thus, it can be concluded that the 9vHPV is highly likely to protect girls 9-15 years of age against the 9 HPV types included in the vaccine and also to protect boys 9-15 years of age against relevant endpoints, i.e. condyloma related to HPV 6 and 11, and anal cancer related to the high-risk types, also based on the efficacy data generated with qHPV (see below, efficacy in males). Concerning the new HPV types, since the 9vHPV vaccine is highly efficacious in preventing HPV 31/33/45/52/58-related cervical, vulvar and vaginal disease, it is reasonable to assume that the 9vHPV vaccine is also efficacious in preventing HPV 31/33/45/52/58-related anal lesions since pathophysiology and mechanisms of protection elicited by HPV vaccination are the same for anal disease as for cervical, vulvar, and vaginal disease.

Efficacy in males 16-26 years of age

Serological non-inferiority in males 16-26 years of age compared to women 16-26 years of age was demonstrated in study 003. Based on the experience with qHPV (efficacy was demonstrated in men 16-26 years of age in reducing the incidence of genital warts and AIN grades 2 and 3) this can be acceptable as a surrogate for clinical protection. The immune responses in the MSM population were lower compared to the general male and female populations. This observation was also made for qHPV, but its clinical relevance is unknown. As for the new HPV types included in 9vHPV, the same reasoning mentioned above for boys apply to men.

Duration of protection

To date, persistence of antibody response induced by the 9vHPV vaccine was demonstrated for up to 3.5 years in women 16-26 years old (study 001), with waining immunity noted for each vaccine type. It is not certain whether individual GMT responses reached their plateau levels, which is the best predictor of durability of protection. In subjects 9-15 years of age, immunogenicity follow-up is available for up to 3 years after vaccination with similar results. Percentage of seropositivity in 9vHPV recipients remained high up to Month 42 in study 001: depending on HPV type, 78-98% of subjects was seropositive. Similar result are seen in adolescent at month 36: depending on HPV type, 93 to 99% of subjects was seropositive.

There is more uncertainty regarding duration of protection for the 5 new HPV types compared to the original 4 HPV types, as there are no previous data for the new types on duration of protection or antibody persistence. In addition the antibody levels appear to be lower than for the 4 original HPV types, however a direct comparison among the GMTs of different virus types is limited by the fact that the amount of antigen for the 5 new virus types in the 9vHPV vaccine is lower compared to the 4 old virus types. Follow-up immunogenicity data, including persistence, are expected from the LTFU extension of studies 001 and 002.

Concomitant vaccinations

Three supportive studies were included in this application. In two studies (005 and 007) the concomitant vaccination of 9vHPV with Adacel and Menactra or Repevax was compared vs. non-concomitant vaccinations. In all studies, the immune responses were satisfactory in the concomitant vaccination groups compared to the non-concomitant vaccination groups. The third study is discussed below.

Data on use of 9vHPV in previous qHPV recipients

In the third supportive study (006), the 9vHPV vaccine was given to prior qHPV recipients. The immune responses to the 4 common HPV types were very high. However, the responses to the 5 new types were low compared to naïve 9vHPV vaccine recipients, which might be theoretically explained with immune interference mechanisms induced by prior vaccination with qHPV. From a clinical point of view, it can be concluded that the immune responses to the four old HPV types 6-11-16-18 following three doses of 9vHPV in qHPV-primed subjects are fully adequate, which means that if a booster vaccination is needed, 9vHPV can be administered. The clinical relevance of the lower immune responses to the 5 new HPV types in qHPV-primed subjects vs. non-primed subjects is unknown.

Claimed indication and posology

The proposed indication for Gardasil 9 is the same as was for Gardasil.

However, the proposed posology differs: the qHPV vaccine now has a 2-dose schedule for 9-13 year olds, which is likely to be used in many national vaccination programs, while the 9vHPV vaccine so far only has data supporting a 3-dose schedule for all age groups. The Applicant has described the plans to study a 2-dose schedule in 9-14 year olds and data are expected approximately 1 year after approval of Gardasil 9. Thus there is a risk of confusion concerning the newly approved 2-dose schedule for Gardasil in 9-13 year olds. The proposed strategy to avoid potential medication errors is considered adequate and was addressed in the RMP (see related section of this report), although a risk of confusing the products and the posologies is inevitable for the transition period.

2.2.8. Conclusions on the clinical efficacy

Efficacy against the 5 new HPV types was demonstrated using a composite clinical endpoint in women aged 16-26 years. It was not planned to demonstrated statistically significant protection against all individual HPV types, or against less common clinical outcomes, which is acceptable given the characteristics of the virus and the pathogenesis of the disease. Nevertheless, because the results were consistent across all endpoints and in light of the supportive analyses conducted, the overall protective efficacy against the new HPV types is considered adequately proven.

Protection against the old HPV types is also considered adequately demonstrated in women 16-26 years of age, considering both clinical and virological outcomes for 9vHPV and qHPV vaccines and exploratory efficacy analyses vs. (historical) qHPV and placebo groups. Serological non-inferiority of 9vHPV vs. qHPV, for which clinical efficacy was already shown in this age group, was demonstrated.

Based on serological comparison to women 16-26 years of age, it can be concluded that the 9vHPV is highly likely to protect girls 9-15 years of age against the 9 HPV types included in the vaccine, and also against relevant endpoints in boys (i.e. condyloma related to HPV 6 and 11, and anal cancer related to the high-risk types). Based on serological comparisons, it can also be concluded that protection against relevant endpoints is highly likely in men 16-26 years of age too.

No data have been provided in HIV infected or immunosuppressed subjects for Gardasil 9. The available data with qHPV have demonstrated that the vaccine is safe and highly immunogenic in HIV-infected children, men and women (>96% children who received qHPV seroconverted to all vaccine types). Given the similar immunogenicity and safety profile of qHPV vs. Gardasil 9 in healthy individual, it is reasonable to infer that Gardasil 9 is safe and immunogenic also in HIV-infected patients. A new study in HIV patients would only confirm a similar or expectedly slightly lower antibody response in subject with adequate HIV treatment vs. healthy

subjects; therefore it is agreed that such study would not provide an added value and it is thus not required. However breakthrough cases in HIV infected individuals should be specifically followed up in future PSURs.

With respect to the clinical program, neither efficacy nor immunogenicity of Gardasil 9 was assessed in women older than 26 years of age. Efficacy can be expected based on the efficacy of qHPV in women 16-45 years of age and on comparable immunogenicity between 9vHPV and qHPV up to 26 years, however the magnitude and durability of vaccine-induced anti-HPV immunity in this age group is unknown, especially for the 5 new vaccine HPV types. However the Applicant committed to conduct a post-marketing immunogenicity and safety study of Gardasil 9 in women 27 to 45 years of age. Based on the proposal assessed, the study should be able to provide adequate evidence in terms of vaccine immunogenicity in this age group. To test for comparison against qHPV is not considered necessary in women 27 to 45 years of age, because equivalent immunogenicity can be extrapolated based on the results obtained in the 9-26 year-olds and because the addition of 5 new types does not affect the responses to the other 4 types.

Given the robustness of the data and the most critical populations studied, the limitations noted when discussing the efficacy and immunogenicity results can be considered secondary. The protective efficacy of Gardasil 9 is overall considered satisfactorily demonstrated in the approved indication.

The CHMP considers the following measures necessary to further confirm the efficacy of the Gardasil 9:

- long term follow up studies to monitor long-term effectiveness and immunogenicity of 9vHPV vaccine and to obtain information on duration of effect in women and adolescents 9-26 years of age.
- A post-marketing immunogenicity and safety study of the 9vHPV vaccine in women 27 to 45 years of age.

These measures are included in the RMP (see RMP section).

Clinical safety

The safety of the 9-valent human papillomavirus (HPV) [Types 6,11,16,18,31,33,45,52,58] L1 Virus-Like Particle [VLP] vaccine (9vHPV vaccine) was assessed in 7 clinical trials conducted in support of this Application. Studies 003, 005, 006, 007, and 009/GDS01C are complete. Extension phases of studies 001 and 002 are ongoing. In each study, investigators were instructed to assess clinical safety, including reviewing adverse events and new medical conditions, at every study visit for all study participants. Briefly, the following safety events were collected in the Phase III studies:

- Injection-site and Systemic Adverse Events occurring Days 1 to 15 following any vaccination and Temperatures Days 1 to 5 following any vaccination were collected using a Vaccination Report Card (VRC) for all study subjects.
- Serious Adverse Events (SAEs) occurring Day 1 through 180 days post-dose 3 (for studies lasting more than 12 months) or Day 1 through end-of-study (for studies of 7-month duration) regardless of causality.
- Deaths and vaccine-related SAEs occurring at any time during the study
- New Medical History, representing medical events that occurred outside the 15 days post-vaccination period and were not reportable as a Serious Adverse Event. New Medical History allowed broad collection of potential safety events including new conditions, symptoms, and laboratory or imaging tests thereby allowing comprehensive safety assessment. New Medical History was collected at every

scheduled study visit for all study subjects for the entire study period; collection of New Medical History occurred at each study visit and was mandatory for all study subjects.

- Pregnancies (including outcomes), lactation, and SAEs occurring in infants born to study participants during the studies were collected for the duration of all studies.

Patient exposure

A total of 23,266 subjects were vaccinated in 7 clinical trials. A total of 15,776 subjects received at least 1 dose of 9vHPV vaccine, and 7391 subjects received at least 1 dose of qHPV vaccine. There were 1,809 males aged 9-15 years; 3,498 females aged 9-15 years; 1,416 males aged 16-26 and 8,053 females aged 16-26 years who received 9vHPV. In contrast, there were 298 females aged 9-15 years and 7,093 females aged 16-26 years receiving qHPV. Given that the qHPV population is less diverse in age and gender, an integrated comparison between 9vHPV and qHPV was not performed. Therefore, the review of the clinical safety database is largely only descriptive in nature.

The study population was predominately white (58.7%) and fairly equally distributed over Europe, Latin America, and North America. Black subjects are less well represented, accounting for only 4.5% of the population that received 9vHPV.

The overall level of health in the study population was high, as expected, with the most commonly reported medical conditions being dysmenorrhea, headache, and seasonal allergies.

3.8% of subjects who received 9vHPV discontinued the trial with only a minority of those being secondary to an adverse event (15 subjects, 0.1%). The proportions of subjects discontinuing the trial were comparable across the demographic groups.

Adverse events

Overall, 90.6% of subjects who received 9vHPV vaccine reported an adverse experience. Most adverse experiences were injection-site adverse experiences (86.2%), and the majority were assessed to be vaccine-related (89.9%).

Injection site events

The proportion of subjects reporting an injection site adverse experience within 5 days of any vaccination was 84.8%. The most common injection site events were pain (83.2%), swelling (36.1%), and erythema (30.8%). 3.6% of all injection site events were reported as severe; the most common event classified as severe was injection site pain.

Over successive doses there was an increase in the incidence of injection site swelling and erythema. Furthermore, there was an increase in reporting of both moderate and severe events.

Systemic events

The proportion of subjects reporting a systemic adverse experience within 15 days of any vaccination was 51.9%; 26.7% of subjects reported at least one systemic event which was considered to be vaccine-related. The most commonly reported events were headache (23.3%), pyrexia (8.2%), and nausea (5.2%).

The proportions of subjects reporting systemic adverse experiences decreased over successive doses.

The majority of subjects experienced adverse experiences which were of mild or moderate severity; however 9.7% reported severe events.

The most commonly reported severe events assessed as vaccine-related are headaches (204 subjects), pyrexia (66 subjects), nausea (40 subjects), and dizziness (27 subjects), all of which are included in the SmPC.

There were a number of severe AEs also assessed as vaccine-related which may be significant based upon their reporting rate relative to those events included in the System Organ Class (SOC): abdominal pain and abdominal pain upper. However there were less than 1% of the total of these events assessed as vaccine-related overall and thus these terms are not included in the SmPC. It appears that the overall reporting of vaccine-related systemic AEs reported to have a severe intensity are consistent with the overall expected adverse event profile.

Events which occurred at an increased frequency compared to all other reported events, and which are not included in the SmPC, include events of abdominal pain (2.0%, 0.6% vaccine-related), abdominal pain upper (2.6%, 0.9% vaccine-related), diarrhoea (2.7%, 0.9% vaccine-related) and vomiting (2.0%, 0.7% vaccine-related). While rates of these events were between 2-3% within 15 days after vaccination, those events assessed as vaccine-related were less than 1% for each term. Furthermore, incidence rates decreased with successive doses of vaccine. The use of medication related to such conditions was constant over successive vaccinations (both pre- and post-vaccination), while rates of abdominal pain/upper abdominal pain decreased. Furthermore, there is data to suggest that these agents were used for other reasons than abdominal pain, such as migraines and headaches. There is no clear evidence to support the need for inclusion of abdominal pain into the SmPC at the present time.

Events which had few or isolated occurrences, but could be linked to potential safety concerns, included events of facial paresis (1 event, vaccine-related), neuralgia (2 events, 1 vaccine-related), sensory disturbance (1 event, vaccine-related), VIIth nerve paralysis (3 events, 2 vaccine-related), vagus nerve disorder (1 event, vaccine-related), sleep disorder (7 events, 1 vaccine-related), butterfly rash (1 event, vaccine-related), hyperhidrosis (24 events, 18 vaccine-related). Regarding the various neurological events, it is acknowledged that the majority of cases did not exhibit a pattern of positive re-challenge, and the assessment of these cases is, overall, reassuring. At the current time, there is not enough data to suggest the need for inclusion of any of the individual events into the SmPC. Review of the cases of hyperhidrosis did not reveal any pattern causing concern and inclusion in the SmPC is not considered warranted.

Serious adverse event/deaths/other significant events

2.5% of subjects reported a serious adverse event. Since the Applicant required that events of foetal loss were to be reported as SAEs, most SAEs were related to pregnancy.

Only 5 SAEs were assessed as related to 9vHPV vaccine: pyrexia, allergy to vaccine, asthmatic crisis, headache and tonsillitis.

There were a number of SAEs occurring in the clinical trial program which are considered adverse events of special interest or are related to previously identified safety concerns: ulcerative colitis, Crohn's disease, multiple sclerosis (2 events), sarcoidosis, intracranial venous thrombosis, deep venous thrombosis, syncope (5 events), and orthostatic hypotension. Upon review these do not raise any new safety concerns. The occurrence of cases of POTS, CRPS, pulmonary vasculitis, and leukaemia are discussed separately below.

Within the clinical safety database for 9vHPV, there are 3 cases of POTS (Postural Tachycardia Syndrome) and 1 case of CRPS (Complex Regional Pain Syndrome), which are both on-going signals identified in the post-marketing period for quadrivalent Gardasil. Both signals have been the subject of extensive assessment in the most recent and previous PSURs for quadrivalent Gardasil. It has been concluded in the recent PSUR procedure (EMEA/H/C/000703/PSUV/0052) that there is currently insufficient evidence to support a possible

causal association between qHPV vaccine and CRPS and POTS. In light of this and given the uncertainty surrounding the background incidence of these syndromes, especially for POTS, these conditions were not included into the RMP. It is instead suggested that these safety concerns are closely monitored within PSURs during the post-marketing period.

One case describes an adolescent subject who was diagnosed with pulmonary vasculitis with a positive antinuclear antibody test (ANA) and for which there was a temporal relationship with receipt of 2 doses of vaccine. The vasculitis was diagnosed based on a pulmonary biopsy but was transient in nature. The case does not fulfil the criteria for a systemic lupus erythematosus (SLE) diagnosis. Low ANA / Anti-dsDNA titres were detected in pre-vaccination serum and could be interpreted as a pre-existing "silent" autoimmune state, which does not exclude a causal relation with 9vHPV vaccine exposure but introduces confounding. Whereas there is a temporal relation, the overall assessment of this case does not warrant inclusion of vasculitis as a potential safety concern into the RMP safety specification.

Finally, there were a total of 5 cases of leukaemia (4 exposed to 9vHPV and 1 exposed to qHPV) in a clinical safety database with 13,360 exposed to 9vHPV. There is a potential concern that the number of observed cases in the study populations could be greater than expected. It is acknowledged that the time to onset in 4-5 cases is prolonged (482-1285 days); however leukaemia may have a prolonged latent phase prior to clinical manifestation of symptoms. Data from the post-marketing experience with qHPV do not show evidence of a signal for leukaemia. However, due to the potential prolonged latency prior to presentation coupled with the underreporting inherent in passive surveillance systems, this might not be unexpected. Multiple reports generally show that infant vaccinations may reduce the risk of subsequent childhood leukaemia. However, these studies have been limited to vaccinations received by infants and young children in routine immunisation programs. There appears to be no report involving older children /adolescents and human papilloma virus vaccination.

Of the five cases of leukaemia, three cases were diagnosed as acute leukaemia and were reported in subjects less than 20 years of age at diagnosis in the 9vHPV groups of studies 001 and 002 (a total of 12,319 person-years) with a time to onset of 27, 482 and 705 days post-dose 3.

Background leukaemia incidence rates are fairly consistent across geographic regions. A reasonable lower and upper bound of acute leukaemia incidence (lymphoid and myeloid combined) in the 10-20 year old age is approximately 2 to 4 per 100,000 person-years. Two of the cases below 20 years of age were acute myeloid leukaemia, while acute lymphoblastic leukaemia is expected to be the most common type in this age group. Time of onset is not very informative for causality assessment for this type of outcome, since long induction times have to be expected.

Whereas the number of cases of leukaemia may be seen as in excess to what is expected, this is based on a few observed cases in relation to a very low background risk for leukaemia in this age group. Such a comparison will inevitably be sensitive to random occurrences of single cases and is not considered sufficient to implicate a causal relation in this case. There is no sufficient evidence to support biological plausibility for a causal relation. While it is considered that the finding is most likely a random occurrence, further reassurance can be gained from the ongoing study program, which will add substantially to the total exposed person-time.

Occurrence of any further cases of leukaemia, with a main focus on the ongoing/planned studies, should be reported as a part of close monitoring of leukaemia in the PSURs.

Deaths

A total of 5 subjects administered 9vHPV vaccine died during the entire study period. Two additional cases have been reported after the data cut-off in the original application. None of the deaths were considered related to the 9vHPV vaccine.

New Medical History

49.8% of subjects reported at least one new medical condition. The most commonly reported new medical conditions were nasopharyngitis (5.7%) and influenza (5.1%). The review of cases with very low frequency "new medical condition" did not reveal any concerns regarding the majority of autoimmune diseases that have been subject to close monitoring, such as rheumatoid arthritis and multiple sclerosis, whose incidence peaks at the age represented in the study population.

Safety in special populations

Age

An increased proportion of female subjects 16-26 years of age experienced injection site events (90.6%) and systemic events (54.2%, 28.2% considered vaccine-related) compared to female subjects 9-15 years of age (injection site events 86.4%; systemic events 49.7%, 25.4% considered vaccine-related).

Gender

In the group 9-15 years of age, females experienced more injection site erythema, pain, and swelling compared to males. However, females and males experienced similar rates of systemic adverse events.

Race / Ethnicity

Overall there were no large differences in the proportions of subjects experiencing adverse events between different racial or ethnicity groups. Black subjects reported fewer local and systemic events but had a higher percentage of subjects recording higher temperatures.

HPV Status at Baseline

There was no difference in the frequency of adverse events between those who were PCR and/or sero-negative and those who were PCR and/or sero-positive to at least 1 of the HPV vaccine type at baseline.

Prior qHPV vaccination

There was an increased proportion of injection site adverse experiences in subjects who received prior qHPV as well as a greater proportion of subjects who discontinued due to an adverse experience (0.5% versus 0.1%). In contrast, the review of new medical history reveals a smaller proportion of subjects who received 9vHPV with a prior qHPV vaccination. There is no difference in the proportion of new medical events potentially related to a systemic autoimmune disease.

Use in pregnancy and lactation

Overall, there were no large differences in pregnancy outcomes between 9vHPV and qHPV nor were there differences based upon baseline HPV status. In Study 001 most of the pregnancy outcomes are known (around 80% for both vaccines). The high foetal loss rate in study 002 in the young women aged 9 to 15 years mostly induced by elective abortion was already reported in the literature. All data regarding pregnancy outcomes were reported and the future pregnancy outcomes will be reported in safety reports.

Use during Lactation

The adverse experience profile in women administered the 9vHPV vaccine who were breastfeeding during the vaccination phase of the clinical studies was generally comparable to the adverse experience profile in the overall Safety Population.

There were no SAEs reported in infants whose mothers were breastfeeding during the vaccination phase of the clinical studies.

Safety related to drug-drug interactions and other interactions

Concomitant medications and contraceptive use

The proportion of subjects who received the 9vHPV vaccine concomitantly with systemic immunosuppressive drugs or with medications with anti-inflammatory/anti-pyretic properties and who reported adverse events, was greater than the proportion of subjects who received the 9vHPV vaccine alone. This pattern was observed for both the 9-15 and the 16-26 year olds. Rates of at least one adverse event were 99.5% and rates of vaccine-related events were 96.6%. It is noted that use of immunosuppressive drugs was prohibited for 3 days prior to receipt of vaccination. The most common uses for these agents (primarily corticosteroids) were for infections, allergies and skin conditions. It is likely that AEs reported for these agents are related to the underlying conditions which they are intended to treat, and that they are reported most commonly post vaccination, given that the use of immunosuppressive drugs was not permitted prior to vaccination. Regarding anti-inflammatory/anti-pyretic therapy it is noted that the use of these products was mostly secondary to the treatment of the common adverse events reported after vaccination (headaches and pyrexia). The increase in systemic AEs observed for subjects receiving either immunosuppressive or anti-inflammatory/anti-pyretic therapy after vaccination are therefore not considered to be a safety concern.

Also, the proportion of vaccinated female subjects 16-26 years old reporting adverse events was greater among those that were concomitantly using hormonal contraceptives compared to those who were not using hormonal contraceptives. Furthermore, it appears that the concomitant use of contraceptives was also linked to a greater proportion of adverse events in the Gastrointestinal disorders SOC (7.1% compared to 5.3%) and in the Nervous System disorders SOC (18.1% compared to 13.5%).

Use with concomitant vaccinations

Overall, concomitant administration with Menactra/Adacel or Repevax was well tolerated. In both studies there was a statistically significant increase in the amount of injection site swelling with the concomitant vaccine administration compared to the single administration. There were no cases of new onset vaccine-related autoimmune disease observed in either study.

Comparative data of 9vHPV and qHPV

Comparative analyses between 9vHPV and qHPV were performed separately for the age groups 9-15 years and 16-26 years.

9-15 years of age

Rates of injection-site adverse experiences were generally comparable between groups receiving 9vHPV and qHPV. However, a higher frequency of injection-site swelling was noted in the 9vHPV vaccine group (47.8%) compared with the qHPV vaccine group (36.0%). The comparison of injection-site adverse reactions showed a statistically significant difference for swelling with a risk difference of 11.8% [95% CI: 3.9; 19.6] between 9vHPV and qHPV.

The frequency of systemic adverse events was slightly lower in the 9vHPV cohort than in the qHPV cohort (20.7% versus 24.3%).

16-26 years of age

A higher frequency of injection-site adverse experiences was noted in the 9vHPV vaccine group (90.8%) compared with the qHPV vaccine group (85.1%). Moreover, injection-site adverse experiences of severe intensity were more frequent in the 9vHPV vaccine group compared with the qHPV vaccine group.

The frequency of systemic adverse events was slightly increased in the 9vHPV cohort compared to the qHPV cohort (55.8% versus 54.9%).

2.2.9. Discussion on clinical safety

Overall, the most commonly occurring adverse events with the 9vHPV vaccine are injection site events. The intensity of these events and the incidence of injection site swelling tended to increase over successive doses of the vaccine. Furthermore, injection site events were observed to be more common with the 9vHPV vaccine compared to the qHPV vaccine, and when the 9vHPV vaccine was administered with concomitant vaccinations. The increased local reactogenicity is more evident in females 16 to 26 years of age compared to both females and males 9 to 15 years of age.

The most commonly reported systemic events were headache and pyrexia.

Three cases coded with the PT of POTS have been reviewed, in light of the on-going review of POTS in the PSURs for qHPV as a potential safety signal. The diagnosis of one of the cases is not clear. The two well characterized cases have both a long time to onset, and are confounded by media attention and stimulated late reporting. At this time, the findings evaluated do not support a possible causal relation between the 9vHPV vaccine and POTS. While the background incidence may be uncertain, report of spontaneous cases are expected simply due to temporal association with vaccination. Continued monitoring within the PSURs is considered warranted as it is for qHPV.

An isolated case of transient pulmonary vasculitis within a plausible time window after vaccination has been thoroughly reviewed. The finding of low ANA / Anti-dsDNA titres before vaccination could be interpreted as a pre-existing "silent" autoimmune state. While there is a temporal relation, the overall assessment points to the conclusion that this case does not warrant inclusion of vasculitis as a potential safety concern in the RMP safety specification. Vasculitis and related conditions should therefore be monitored within the PSURs but presently no other regulatory action is considered warranted.

Five cases (4 with 9vHPV vaccine and 1 with qHPV vaccine) of acute leukaemia have been reported, three of which occurred in subjects younger than 20 years of age at diagnosis. While the observed number of cases of leukaemia exceeded the expected number of cases, this observation is based on a few cases in relation to a very low background risk for leukaemia in this age group. Such a comparison will inevitably be sensitive to random occurrences of single cases and it is not considered sufficient to implicate a causal relation at this stage. There is no sufficient evidence to support a biological plausibility for a causal relation. While it is considered that the finding is most likely a random occurrence, further reassurance can be gained from the ongoing study program, which will add substantially to the total exposed person-time. Occurrence of any further cases of leukaemia, with a main focus on the ongoing/planned studies, should be reported as a part of close monitoring of leukaemia in PSURs.

Overall, reported pregnancy outcomes were as expected in line with the normal background for the treated population. A large amount of data (more than 1000 pregnancy outcomes) indicates no malformative nor foeto/ neonatal toxicity. However, the data are not considered sufficient to recommend the use of Gardasil 9 during pregnancy.

9vHPV vaccine was administered to a limited number of breastfeeding women. There were no serious adverse events reported in subjects who were breastfeeding during the vaccination period. The safety profile in breastfeeding women was comparable to that of women in the overall safety population.

Gardasil 9 was not studied in immunocompromised subjects but from a safety perspective this does not represent an issue, since safety is expected to be the same as in a healthy population.

Study 003 in males 16-26 years of age was assessed separately as it was provided during the procedure. The safety results are briefly summarized as follows:

- The proportion of subjects reporting at least one adverse experience, injection-site adverse experience, or systemic adverse experience within 15 days of any vaccination was numerically lower in 16-26 year-old males (HM and MSM) compared to 16-26 year-old females.
- Five subjects (2 men and 3 women) discontinued from the study due to vaccine-related adverse experience.
- Forty-nine (49) subjects (23 men, 26 women) reported SAEs during the entire course of the study. There were no vaccine-related SAEs.
- No subject died during the entire course of the study.

No new safety concern was raised by the safety data in this study. The results from study 003 are in line with the other studies.

From the safety database all the adverse reactions reported after the 9vHPV vaccine in clinical trials and post-marketing for qHPV have been included in the Summary of Product Characteristics.

Assessment of paediatric data on clinical safety

From the safety database all the adverse reactions reported after the 9vHPV vaccine in clinical trials and post-marketing for qHPV have been included in the Summary of Product Characteristics.

2.2.10. Conclusions on the clinical safety

Overall, the most commonly occurring AEs with the 9vHPV vaccine are injection site events, whose intensity and incidence tended to increase over successive doses of the vaccine. The systemic events most commonly reported were headache and pyrexia.

2.5% of subjects reported a serious adverse event. Only 5 SAEs were assessed as related to 9vHPV vaccine: pyrexia, allergy to vaccine, asthmatic crisis, headache and tonsillitis.

There was one case of pulmonary vasculitis and few cases of leukaemia, which upon assessment do not constitute sufficient evidence to raise a specific safety concern at the moment. In addition, within the clinical safety database for Gardasil 9 three cases of POTS and 1 case of CRPS were reported, and both are on-going signals identified in the post-marketing period for qHPV. Overall the low number of SAEs reported and the confounding associated with the reported cases indicate that there is no signal ongoing for Gardasil 9, but nevertheless given the seriousness of the conditions, they should be closely monitored in future PSURs.

Concerning the use in pregnancy, although the assessment of pregnancy outcomes so far did not raise any safety concern, since the data are sparse the use of Gardasil 9 is not recommended during pregnancy. The safety profile of Gardasil 9 in breastfeeding women is acceptable.

In conclusions, Gardasil 9 was well tolerated in the population studied and the overall safety profile of the vaccine is considered acceptable. Long term follow up studies are outstanding at present. The Applicant will submit the results as indicated in the RMP (see RMP section).

Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 1.2 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

The applicant implemented the changes in the RMP as requested by PRAC.

The CHMP endorsed the Risk Management Plan version 1.4 with the following content:

Safety concerns

Important identified risks	• Hypersensitivity (Type 1)
Important potential risks	• Product confusion between Gardasil and Gardasil®9 • Mixed regimen between Gardasil/ Silgard and Gardasil®9
Missing information	• Long term effectiveness and immunogenicity • Exposure during Pregnancy • Viral type replacement • Immunogenicity and safety in females greater than 26 years of age

Pharmacovigilance plan

Study / Activity	Objectives	Safety Concerns Addressed	Status	Date for Submission of Interim / Final Reports (target dates)

Pregnancy Registry (category 3)	To monitor pregnancy outcomes in women exposed to 9vHPV vaccine during pregnancy.	Exposure to vaccine during pregnancy	Planned	**Interim Reports:** 31-AUG-2016 31-AUG-2017 31-AUG-2018 31-AUG-2019 31-AUG-2020 **Final Report:** ~18 months after enrolment of the last patient.
V503-021 Nordic Long-term Follow-Up Study (10-Year extension in subjects from V503-001) (category 3)	To monitor the long term safety of 9vHPVvaccine To monitor long-term effectiveness and immunogenicity of 9vHPV vaccine To obtain information on duration of effect	Viral type replacement Long-term Effectiveness/ Immunogenicity	Planned	**Interim Reports:** ~4Q2017 ~4Q2019 ~4Q2021 ~4Q2023 **Final Report Submission:** ~31-Dec-2026
V503-002-20 Adolescent Long-term Follow-Up Study (10-Year Post-dose 3 Extension) (category 3)	To monitor long-term effectiveness and immunogenicity of 9vHPV vaccine To obtain information on duration of effect	Long-term Effectiveness/ Immunogenicity	Planned	**Interim 72-Month Report:** ~4Q2017 **Interim 96 Month Report:** ~4Q2019 **Final Report Submission:** ~31-Mar-2023
A post-marketing immunogenicity and safety study of the 9vHPV vaccine in women 27 to 45 years of age	- To demonstrate immunogenicity for each of the 9 vaccine HPV types in women 27 to 45 years of age. - To collect data on the safety profile of 9vHPV vaccine in women 27 to 45 years	Immunogenicity and safety in females greater than 26 years of age	Planned	Final Report: ~1Q 2019

Risk minimisation measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important Identified Risks		
Hypersensitivity (Type	Hypersensitivity to Gardasil or Gardasil 9 vaccines' components is included as a contraindication in section	None

1)	4.3; hypersensitivity reactions including anaphylactic/ anaphylactoid reactions are also included as an ADR reported during post-approval use of qHPV vaccine, in section 4.8 of the SmPC.	
Important Potential Risks		
Product confusion between Gardasil and Gardasil®9	Distinctive name and packaging of product The MAH, in agreement and in consultation with Member States' National Competent Authorities, will consider whether nationally specific and healthcare system specific additional measures are required (e.g. communication to HCPs - prescribers and vaccinators - regarding distinctive characteristics between 9vHPV vaccine and qHPV vaccine.	None
Mixed regimen between Gardasil/ Silgard and Gardasil®9	Text is included in the SmPC to indicate that Gardasil9 is not interchangeable with other HPV vaccines and that studies using a mixed regimen of HPV vaccines were not performed for Gardasil9 (Section 4.2 and 4.4). The MAH, in agreement and in consultation with Member States' National Competent Authorities, will consider whether nationally specific and healthcare system specific additional measures are required (e.g. communication to HCPs - prescribers and vaccinators - regarding distinctive characteristics between 9vHPV vaccine and qHPV vaccine.	None
Missing Information		
Exposure during pregnancy	SmPC Section 4.6 Fertility, pregnancy and lactation includes language stating that Gardasil 9 is not recommended for use during pregnancy.	None
Long-term effectiveness and immunogenicity	None	None
Viral type replacement	None	None
Immunogenicity and safety in females greater than 26 years of age	None	None

Product information - User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Gardasil 9 is a ninevalent vaccine against premalignant lesions and cancers affecting the cervix, vulva, vagina and anus, and external genital warts caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58. Gardasil 9 contains 5 new HPV types compared to a qHPV vaccine. Considering that it is not possible to investigate efficacy in boys or girls 9-15 years of age due to sexual naivety, the agreed strategy to demonstrate the efficacy of the vaccine was to generate efficacy data in 16-26 years old women and to extrapolate this data to younger subjects based on immunogenicity (bridging) data. This approach was already proved valuable for previously authorised HPV vaccines.

Overall, efficacy against the 5 new HPV types has been demonstrated in 16-26 year old women based on a composite clinical efficacy endpoint and on immunogenicity data. Efficacy in women 16-26 years against the old HPV types 16, 18, 11 and 6 (also present in qHPV) was extrapolated on the basis of serological non-inferiority, which was demonstrated by comparing immunological responses of individuals vaccinated with 9vHPV to individuals vaccinated with qHPV in the same age group. Additionally no evidence for a negative trend in protection against clinical endpoints was identified in study 001 for the old HPV types, supporting the immunogenicity results. In fact, there were fewer cases of disease endpoints related to HPV 16/18 in the 9vHPV group compared to the qHPV group. There were slightly more cases of disease endpoints (condyloma) related to HPV 6/11 (low-risk types for cancer, but causing condyloma) in the 9vHPV group compared to the qHPV group, but there is still a relevant protection.

For girls and boys 9-15 years of age, serological non-inferiority for all HPV types was demonstrated compared to women 16-26 who received 9vHPV (study 002). In addition, serological non-inferiority for the old HPV types was demonstrated in girls receiving 9vHPV compared to girls of the same age group receiving qHPV (study 009/GDS01C).

Concerning demonstration of efficacy in the male population against relevant endpoints (i.e. premalignant anal lesions and anal cancer), the Applicant submitted during the evaluation the final results of an immunogenicity and safety study conducted in women and in men 16-26 years of age vaccinated with 9vHPV (study 003). This study was designed to extend the efficacy observed in females 16 to 26 years of age to males 16 to 26 years of age based on immunological bridging. The results indicate that Gardasil 9 is equally immunogenic and has a similar safety profile in both sexes, thus allowing to conclude that Gardasil 9 is expected to be efficacious against premalignant lesions and cancers of the anus in females as well as in males. Up to 90% of the cases of anal cancers worldwide are attributable to HPV types 6-11-16 and 18.

Long term follow up (for 10 years after protocol completion of the primary study) for breakthrough disease cases is expected post-authorisation for Gardasil 9. Long term effectiveness is being assessed in long-term follow-up of clinical study cohorts for qHPV vaccines. Interim analyses showed no breakthrough of HPV-related disease after up to 6 years of follow-up.

Uncertainty in the knowledge about the beneficial effects

The incremental efficacy of Gardasil 9 relative to qHPV was demonstrated for the composite efficacy endpoint, with most endpoint cases diagnosed as CIN2. The cases of CIN3 were few, but statistically significant protection against CIN3 related to the 5 new HPV types was demonstrated. The incremental benefit of Gardasil 9 against AIS and VIN2/3 surrogate endpoints has not been established.

Efficacy for specific HPV types was demonstrated only against HPV types 31, 33 and 52, because there were insufficient numbers of cases against two of the new HPV types (45 and 58) to demonstrate statistically significant protection for these. However, there was no negative trend in protective efficacy across virus types as indicated by secondary and exploratory efficacy analysis against disease endpoints, and the results were consistent across all endpoints. In addition the antibody GMTs were high against all HPV vaccine types and, although there is currently no serological correlate of protection established, it is generally agreed that circulating specific antibodies are associated with the likely protective mechanism induced by the vaccine. Therefore, looking at the totality of the existing data, it is considered reasonable to assume that 9vHPV provides protection against all individual new HPV types.

Gardasil 9 did not confer apparent protection against non-vaccine HPV types. It is not immediately clear whether the widespread use of Gardasil 9 will result in increase of disease caused by non-vaccine HPV types, although this is considered a theoretical concern based on the present experience with Gardasil, since no signs of HPV type replacements have been observed so far. This theoretical concern will be addressed in the Nordic Long-term Follow-Up Study V503-021 (10-Year extension in subjects from the efficacy study 001).

The antibody persistence data assessed so far have demonstrated a similar pattern compared to authorised HPV vaccines, i.e. antibody levels increased substantially upon vaccination followed by a decline to a plateau level, with very slow further decline thereafter. The available data include immunogenicity follow-up up to 3.5 years in women 16-26, and 3 years in boys and girls 9-15 years of age, and longer follow-up is planned (up to 10 additional years in the LTFU extension of study 001 and 002). The uncertainty is mostly related to the 5 new HPV types, as no previous data for these types exist on duration of protection or antibody persistence, and their antibody levels appear to be lower than those for the 4 old HPV types. The Applicant committed to generate new data post-authorisation to further investigate this (LTFU studies V503-021 and V503-002-20).

The observed 20% decrease in anti-HPV 11 immune responses induced by Gardasil 9 compared to qHPV in young women could raise a similar concern of waning immunity; however the protection afforded by Gardasil 9 against HPV 11 has been adequate so far, which is reassuring.

Gardasil 9 efficacy and immunogenicity were not assessed in women older than 26 years of age. Thus, the magnitude and durability of vaccine-induced anti-HPV immunity in this age group is unknown, especially for the 5 new vaccine HPV types. The Applicant committed to conduct a post-marketing immunogenicity and safety study of Gardasil 9 in women 27 to 45 years of age.

Concerning demonstration of efficacy in the male population, in addition to the data already available from study 003, a new study is ongoing to demonstrate that anti-HPV responses to 9vHPV are non-inferior to anti-HPV responses to qHPV in males 16 to 26 years of age. One phase III study of qHPV vaccine in males 16 to 26 years of age showed that qHPV vaccine prevented persistent infection and disease due to HPV vaccine types in this study population (Giuliano/Palefsky et al., *N Engl J Med* 2011; Palefsky/Giuliano et al *N Engl J Med* 2011). Therefore the new immunogenicity data will allow to bridge efficacy data from qHPV to 9vHPV to further confirm the current knowledge and expectations for Gardasil 9 efficacy in males.

No data have been provided in HIV infected or immunosuppressed subjects for Gardasil 9, but available data with qHPV show that the vaccine is safe and highly immunogenic in HIV-infected children, men and women (>96% children who received qHPV seroconverted to all vaccine types). Based on this, it is reasonable to infer that Gardasil 9 is safe and immunogenic also in HIV-infected patients. A new study in HIV patients is not required but breakthrough cases in HIV infected individuals should be specifically followed up in PSURs.

Risks

Unfavourable effects

Injection site events were reported by > 80% of clinical trial subjects, the most commonly reported were injection site pain and injection site swelling. Injection site events occur more commonly than with qHPV, as expected due the higher antigen content of the 9vHPV vaccine. Furthermore, the intensity of injection site events tended to increase over successive doses as did the incidence of injection site swelling. No new major safety concern has been identified. The most commonly reported systemic events were headache and pyrexia. Pyrexia was reported as adverse event in 8.2% of subjects receiving the vaccine in the pooled safety analysis from 7 studies (>15,000 subjects), whereas only one report of pyrexia as SAE was observed.

Uncertainty in the knowledge about the unfavourable effects

The remaining safety concerns relate to the risk of rare unexpected adverse events.

Five cases (4 with 9vHPV and 1 with qHPV) of acute leukaemia have been reported, three in subjects younger than 20 years of age at diagnosis. While the observed number of cases of leukaemia exceeded the expected number of cases, this is based on a few observed cases in relation to a very low background risk for leukaemia in this age group. Such a comparison will inevitably be sensitive to random occurrences of single cases and is not considered sufficient to implicate a causal relation in this case. In addition there is no substantial evidence to support biological plausibility for a causal relationship. While it is considered that the finding is most likely a random occurrence, further reassurance can be gained from the ongoing study program (2 long term follow up studies will run for 10 years, in addition to post-marketing pharmacovigilance and PSUR monitoring), which will add substantially to the total exposed person-time.

Benefit-risk balance

Importance of favourable and unfavourable effects

HPV infection causes benign and malignant diseases localized in the anogenital area and the aerodigestive tract, in both men and women. Gardasil 9 provides broader cancer coverage than qHPV, and is anticipated to prevent ~90% of cervical cancer and 75-85% of premalignant cervical lesions, 85-90% of vulvar cancer and 90-95% of premalignant vulvar lesions, 80-85% of vaginal cancer and 75-85% of premalignant vaginal lesions, and 90% of external genital warts.

It is considered most important that Gardasil 9 is able to provide protection against disease endpoints related to HV 16 and 18 at least to the same extent as seen for Gardasil, because HPV 16 and 18 are by far the most common high-risk HPV types. The protection against disease caused by HPV 6 and 11, which is mainly condyloma, is also considered important but to a lesser extent than protection against HPV types 16/18, since condyloma is a disease with non-serious consequences.

The protection against the 5 new types is considered important because these are also high-risk HPV types, although each one of them is less common in cancers and pre-cancerous lesions than 16 and 18 types.

Gardasil 9 exhibits a high percentage of injection-related local adverse events, specifically injection site pain and swelling; however numbers are only slightly elevated vs. approved qHPV vaccines. Furthermore, the intensity of the injection site events showed a tendency to increase over successive doses as did the incidence of injection site swelling. Such events are of limited clinical relevance.

	Effect	Short Description	Unit	9vHPV	control	Additional Clarifications	References
Favourable	Protection against new HPV types-related disease	HPV 31/33/45/52/58-Related CIN 2/3, AIS, Cervical Cancer, VIN 2/3, VaIN 2/3, Vulvar Cancer, and Vaginal Cancer	Protective efficacy: 96.7% (95% CI): 80.9%, 99.8%	9vHPV	qHPV	Efficacy studied in women 16-26 years. No trend of less protection against HPV 16/18 disease compared to Gardasil. Serological bridging to 9-15 years old boys and girls.	Study 001 (n=7000/arm)
	Protection against HPV types 6-11-16-18	Comparison of immune responses based on cLIA titres (GMTs at M7) between 9v-HPV vs. qHPV Non-inferiority for GMTs is defined as the lower bound of the two-sided 95% confidence interval for the GMT ratio of 9-valent vaccine vs. qHPV being greater than 0.67	Geometric Mean Titre (GMT) ratio (95% CI)	Anti-HPV6 1.02 (0.99, 1.06) Anti-HPV11 0.80 (0.77, 0.83) Anti-HPV16 0.99 (0.96, 1.03) Anti-HPV18 1.19 (1.14, 1.23)			
Unfavourable	Injection-related local reactions	Adverse events coded with the Preferred Term beginning "Injection site X"	Proportion of females 9-15y or 16-26y who had at least 1 or more injection site AE	91.6% 90.8%	88.3% 85.1%	No comparison between 9vHPV and qHPV was made on pooled data. The presented figures are from individual studies.	Study 009/GDS01C for girls 9-15 years (n=300/arm) Study 001 for women 16-26 (n=7000/arm)
	Systemic adverse reactions	Adverse events in any system organ class assessed as vaccine-related	Proportion of girls 9-15y who had at least 1 or more	20.7%	24.3%		

			systemic AE				
	Systemic adverse reactions	Adverse events in any system organ class assessed as vaccine-related	Proportion of women 16-26 who had at least 1 or more systemic AE	29.5%	27.3%		
	Serious Adverse Events	Overall SAEs regardless of causality for study 001 (n=7000)	Proportion of women 16-26 years of age with one or more serious adverse events	3.3%	2.6%		
	Serious Adverse Reactions	Vaccine-related Serious Adverse Events in the pooled safety analysis of 13.000 sbj (6 studies)	Proportion of sbj 9-26 years of age	<0% (5subj)	N/A	S-ADRs: pyrexia, allergy to vaccine, asthmatic crisis, headache, and tonsillitis	

Benefit-risk balance

The benefit-risk balance for Gardasil 9 is overall positive.

Discussion on the benefit-risk balance

The most important beneficial effect of Gardasil 9 is the protection against disease caused by HPV types 16 and 18, which is maintained both in females and in males as compared to qHPV. This was demonstrated based on lack of negative trend in clinical outcomes, and on serological bridging between qHPV and 9vHPV in women 16-26 years of age. The immune responses to the old HPV types (6, 11, 16 and 18) were non-inferior in the 9vHPV group compared to the qHPV group, which allowed for extrapolation of the efficacy data previously established for qHPV vaccine in the same age group.

The added protection against the 5 new HPV types was also demonstrated. A composite endpoint of several relevant disease endpoints related to any of the 5 new types was chosen for the primary analysis. In addition immunogenicity data confirmed the protective efficacy.

The majority of subjects who received Gardasil 9 experienced injection-site related adverse events which tended to increase in intensity over successive doses. The safety profile of Gardasil 9 is considered acceptable, although there is a slightly higher risk of local and systemic reactions compared to qHPV.

Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Gardasil 9 in the prophylaxis of the following HPV diseases:

- Premalignant lesions and cancers affecting the cervix, vulva, vagina and anus caused by vaccine HPV types
- Genital warts (Condyloma acuminate) caused by specific HPV types

is favourable, and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription

Official batch release

In accordance with Article 114 Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that the active substances Human Papillomavirus Type 31 L1 protein, Human Papillomavirus Type 33 L1 protein, Human Papillomavirus Type 45 L1 protein, Human Papillomavirus Type 52 L1 protein and Human Papillomavirus Type 58 L1 protein are qualified as new active substances.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0196/2013 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.