



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 November 2014
EMA/128923/2015
Committee for Medicinal Products for Human Use (CHMP)

Gardasil/Silgard

human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed)

CHMP assessment report for paediatric use studies
submitted according to Article 46 of the Regulation (EC)
No 1901/2006

Assessment report as adopted by the CHMP with
all commercially confidential information deleted



1. Introduction

On September 5, 2014, the MAH submitted a completed paediatric study for Gardasil/Silgard, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that "V503 – 001: A 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" is part of a clinical development program for V503, for which an MAA has been submitted earlier this year. Gardasil is being used as comparator in this study.

2.2. Information on the pharmaceutical formulation used in the study

The commercial formulation was used in the study.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- V503 – 001: A 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

2.3.2. Clinical study

V503 – 001: A 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

Description

This was a randomized, double-blind (operating under in-house blinding procedures), controlled with qHPV vaccine, multicenter, multinational, dose-ranging, safety, immunogenicity and efficacy study with a target enrollment of 14,620 subjects. The study was enrolled in 2 parts. Approximately 1240 subjects were to be enrolled in Part A and equally randomized to 3 dose formulations of 9vHPV vaccine or qHPV vaccine. One dose formulation was selected based on interim immunogenicity results. Approximately 13,380 subjects were to be enrolled in Part B and equally randomized to the selected dose formulation of 9vHPV vaccine or qHPV vaccine.

Assessor's comment: The current study is also being assessed within the MAA for V503 (EMA/H/C/3852). Thus, the description of this study is copied from the AR for V503.

Methods

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.

Study design

Randomized, double-blind, controlled with qHPV vaccine, multicenter, multinational dose-ranging, safety, immunogenicity and efficacy study.

Study population /Sample size

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 enrollment 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.

Treatments

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.

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.

Outcomes/endpoints

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) cervicovaginal 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.

Immunogenicity: Serum anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 titers 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 titers for each of the vaccine HPV types; 2) seroconversion status (i.e., above or below serostatus cutoff) 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.

Safety:

Results

Recruitment/ Number analysed

The study participant distribution is summarised in Tables 10-1, 10-2, 10-3, 10-4 and 10-5.

Table 10-1. Disposition of Subjects (Day 1 to Month 7) (All Randomized Subjects, Dose-Ranging Substudy)

	Low-Dose 9vHPV Vaccine n (%)	Mid-Dose 9vHPV Vaccine n (%)	High-Dose 9vHPV Vaccine n (%)	qHPV Vaccine n (%)	Total n (%)
Subjects in population				310	
Vaccinated at					
Vaccination 1				310 (100.0)	
Vaccination 2				305 (98.4)	
Vaccination 3				300 (96.8)	
Trial Disposition					
Completed				297 (95.8)	
Discontinued				13 (4.2)	
Adverse Event				0 (0.0)	
Lost To Follow-Up				7 (2.3)	
Protocol Violation				1 (0.3)	
Withdrawal By Subject				5 (1.6)	
Subject Study Medication Disposition					
Completed				300 (96.8)	
Did Not Take Study Medication				0 (0.0)	
Discontinued				10 (3.2)	
Adverse Event				0 (0.0)	
Lost To Follow-Up				5 (1.6)	
Pregnancy				1 (0.3)	
Protocol Violation				1 (0.3)	
Withdrawal By Subject				3 (1.0)	
Protocol Milestone					
Continuing Into Next Trial Segment				297 (95.8)	
Not Continuing Into Next Trial Segment				1 (0.3)	
Unknown				12 (3.9)	
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.					

Table 10-2. Disposition of Subjects (Day 1 to Month 7) (All Randomized Subjects, Efficacy Substudy)

	9vHPV Vaccine		qHPV Vaccine	
	n	(%)	n	(%)
Subjects in population	7,106		7,109	
Vaccinated at				
Vaccination 1	7,099	(99.9)	7,105	(99.9)
Vaccination 2	7,015	(98.7)	7,015	(98.7)
Vaccination 3	6,928	(97.5)	6,934	(97.5)
Trial Disposition				
Completed			6,854	(96.4)
Discontinued			255	(3.6)
Adverse Event			2	(0.0)
Lost To Follow-Up			128	(1.8)
Physician Decision			2	(0.0)
Protocol Violation			4	(0.1)
Withdrawal By Subject			119	(1.7)
Subject Study Medication Disposition				
Completed			6,934	(97.5)
Did Not Take Study Medication			4	(0.1)
Discontinued			171	(2.4)
Adverse Event			1	(0.1)
Lost To Follow-Up			81	(1.1)
Physician Decision			4	(0.1)
Pregnancy			1	(0.0)
Protocol Violation			4	(0.1)
Withdrawal By Subject			77	(1.1)
Protocol Milestone				
Continuing Into Next Trial Segment	6,857	(96.5)	6,852	(96.4)
Not Continuing Into Next Trial Segment			8	(0.1)
Unknown			249	(3.5)
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.				

Table 10-3 Disposition of Subjects (> Month 7 to Month 42) (All Randomized Subjects, Efficacy Substudy)

	9vHPV Vaccine n (%)	qHPV Vaccine n (%)	Total n (%)
Subjects in population		6,124	
Trial Disposition			
Completed		5,542 (90.5)	
Discontinued		582 (9.5)	
Adverse Event		3 (0.0)	
Lost To Follow-Up		301 (4.9)	
Physician Decision		3 (0.0)	
Protocol Violation		2 (0.0)	
Withdrawal By Subject		273 (4.5)	
Protocol Milestone			
Continuing Into Next Trial Segment		5,176 (84.5)	
Not Continuing Into Next Trial Segment		334 (5.5)	
Unknown		614 (10.0)	
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 10-4 Disposition of Subjects (> Month 42 to Month 48) (All Randomized Subjects, Efficacy Substudy)

	9vHPV Vaccine n (%)	qHPV Vaccine n (%)	Total n (%)
Subjects in population		3,552	
Trial Disposition			
Completed		3,528 (99.3)	
Discontinued		24 (0.7)	
Adverse Event		1 (0.0)	
Lost To Follow-Up		5 (0.1)	
Pregnancy		1 (0.0)	
Withdrawal By Subject		17 (0.5)	
Protocol Milestone			
Continuing Into Next Trial Segment		3,519 (99.1)	
Not Continuing Into Next Trial Segment		9 (0.3)	
Unknown		24 (0.7)	
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 10-5 Disposition of Subjects (> Month 48 to Month 54) (All Randomized Subjects, Efficacy Substudy)

	9vHPV Vaccine n (%)	qHPV Vaccine n (%)	Total n (%)
Subjects in population		818	
Trial Disposition			
Completed		813 (99.4)	
Discontinued		5 (0.6)	
Lost To Follow-Up		3 (0.4)	
Withdrawal By Subject		2 (0.2)	
Protocol Milestone			
Continuing Into Next Trial Segment		310 (37.9)	
Not Continuing Into Next Trial Segment		504 (61.6)	
Unknown		4 (0.5)	
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.			

Efficacy results

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

Table 11-1 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. The cumulative incidence distribution of the primary efficacy endpoint in the PPE population is shown in Figure 11-1.

Table 11-2 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.

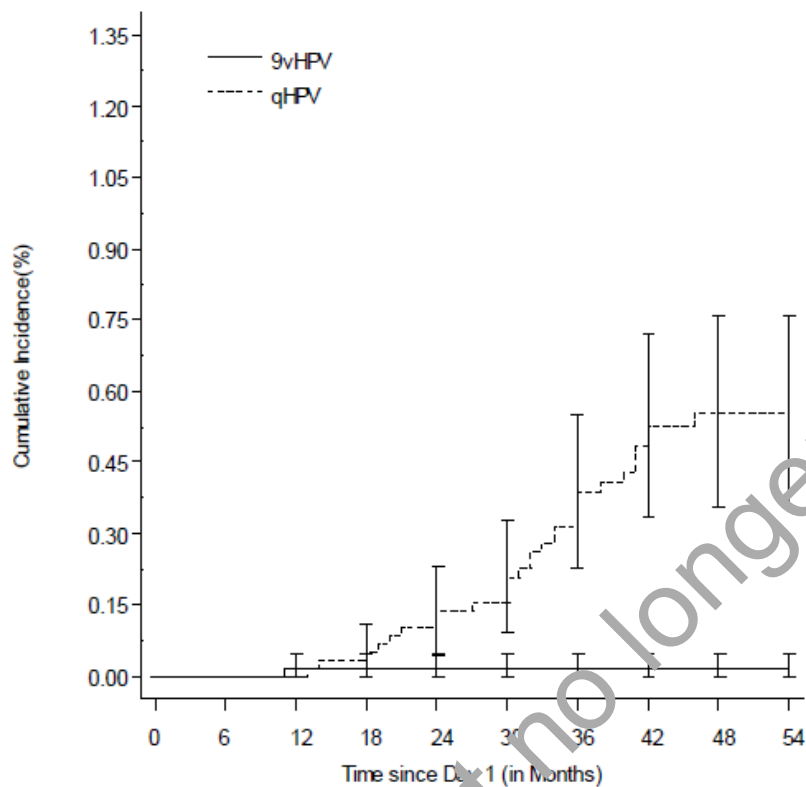
One of the secondary objective was efficacy against HPV 31/33/45/52/58-Related Cervical, Vulvar, and Vaginal Disease, i.e the same as the primary objective, but also including low-grade disease. The efficacy against this composite endpoint was 97.1% (95% CI 91.9; 99.2).

Table 11-1 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 (Per-Protocol Efficacy Analysis Population)

Endpoint	9vHPV Vaccine (N=7,105)				qHPV Vaccine (N=7,105)				Observed Efficacy (%)	95% CI	P-value [†]
	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			
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			6,017	30	18,976.6	0.2	96.7	(88.9, 99.8)	
By HPV Type											
HPV 31-Related						7	16,560.7	0.0			
HPV 33-Related						7	17,803.5	0.0			
HPV 45-Related						2	18,079.2	0.0			
HPV 52-Related						11	16,473.6	0.1			
HPV 58-Related						6	16,842.4	0.0			
By Lesion Type											
CIN 2 or worse	5,948	1	17,407.0		5,943	27	17,427.2	0.2	96.3	(79.5, 99.8)	
CIN 2/3						27	17,427.2	0.2			
or AIS						27	17,427.2	0.2			
CIN 2/3						23	17,430.9	0.1			
CIN 2						5	17,438.1	0.0			
CIN 3						0	17,441.7	0.0			
AIS											
Cervical Cancer						0	17,441.7	0.0			
VIN 2/3 or worse	6,009	0			6,012	3	18,988.0	0.0	100	(-71.5, 100)	
VIN 2/3 or worse						0	18,991.0	0.0			
VIN 2/3						0	18,991.0	0.0			
Vulvar Cancer						0	18,991.0	0.0			
VaIN 2/3 or worse						3	18,988.0	0.0			
VaIN 2/3						3	18,988.0	0.0			
Vaginal Cancer						0	18,991.0	0.0			

[†] 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

Figure 11-1. 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 (Per-Protocol Efficacy Analysis Population)



Subjects at Risk										
9vHPV	6016	6016	5941	5826	5715	5579	5404	4267	1678	425
qHPV	6017	6017	5926	5816	5693	5572	5400	4294	1708	419
Cumulative Cases										
9vHPV	0	0	1	1	1	1	1	1	1	1
qHPV	0	0	1	3	8	12	22	29	30	30

Table 11-2 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 (HPV-Naive Type-Specific Analysis Population)

Endpoint	9vHPV Vaccine		qHPV Vaccine (N=7,105)		Incidence Rate per 100 Person- Years at Risk	Observed Efficacy (%)	95% CI
	n	Number of Cases	Person- Years at Risk	Person- Years at Risk			
HPV 31/33/45/52/58-Related CIN 2/3, AIS, Cervical Cancer, VIN 2/3, VaIN 2/3, Vulvar Cancer, and Vaginal Cancer	6,866	42	24,668.0	0.2			
By HPV Type							
HPV 31-Related	6,104	12	21,917.7	0.1			
HPV 33-Related	6,467	8	23,293.2	0.0			
HPV 45-Related	6,571	3	23,663.4	0.0			
HPV 52-Related	6,129	17	22,063.3	0.1			
HPV 58-Related	6,193	9	22,253.0	0.0			
By Lesion Type							
CIN 2 or worse	6,718	39	22,867.2	0.2			
CIN 2/3 or AIS	6,718	39	22,867.2	0.2			
CIN 2/3	6,718	39	22,867.2	0.2			
CIN 2	6,718	33	22,871.4	0.1			
CIN 3	6,718	9	22,884.6	0.0			
AIS	6,718	0	22,888.9	0.0			
Cervical Cancer	6,718	0	22,888.9	0.0			
VIN 2/3 or VaIN 2/3 or worse	6,865	3	24,700.5	0.0			
VIN 2/3 or worse	6,865	0	24,703.5	0.0			
VIN 2/3	6,865	0	24,703.5	0.0			
Vulvar Cancer	6,865	0	24,703.5	0.0			
VaIN 2/3 or worse	6,865	3	24,700.5	0.0			
VaIN 2/3	6,865	0	24,700.5	0.0			
Vaginal Cancer	6,865	0	24,703.5	0.0			

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 11-5 presents the results of evaluation of efficacy against persistent infection related to HPV types 31, 33, 45, 52, and 58 in the PPE and INTS 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 11-5 Analysis of Efficacy Against HPV 31/33/45/52/58-Related Persistent Infection (PPE and HN-TS Analysis Populations)

Analysis Population Endpoint	9vHPV Vaccine				qHPV Vaccine (N=7,105)						
	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			
Per-Protocol Efficacy (PPE)											
Persistent Infection ≥6 Months [†]											
HPV 31/33/45/52/58-Related	5,939	35			5,953	810	15,451.6	5.2	96.0	(94.4, 97.2)	
HPV 31-Related					5,198	150	14,316.9	1.0			
HPV 33-Related					5,560	106	15,416.9	0.7			
HPV 45-Related					5,658	124	15,633.4	0.8			
HPV 52-Related					5,160	387	13,885.7	2.8			
HPV 58-Related					5,284	225	14,404.9	1.6			
Persistent Infection ≥12 Months [†]											
HPV 31/33/45/52/58-Related					5,953	544	15,761.9	3.5			
HPV 31-Related					5,198	97	14,374.1	0.7			
HPV 33-Related					5,560	79	15,452.5	0.5			
HPV 45-Related					5,658	73	15,686.8	0.5			
HPV 52-Related					5,160	238	14,063.3	1.7			
HPV 58-Related					5,284	145	14,553.4	1.0			
HPV-Naïve Type-Specific (HN-TS)											
Persistent Infection ≥6 Months [†]											
HPV 31/33/45/52/58-Related				0.7	6,699	1,150	19,998.4	5.8			
HPV 31-Related				0.2	5,953	234	19,150.7	1.2			
HPV 33-Related				0.1	6,314	152	20,486.1	0.7			
HPV 45-Related				0.1	6,412	170	20,783.2	0.8			
HPV 52-Related				0.3	5,983	552	18,742.8	2.9			
HPV 58-Related				0.2	6,040	324	19,310.6	1.7			
Persistent Infection ≥12 Months [†]											
HPV 31/33/45/52/58-Related				0.5	6,699	802	20,509.3	3.9			
HPV 31-Related				0.1	5,953	159	19,263.8	0.8			
HPV 33-Related				0.1	6,314	109	20,550.3	0.5			

Related HPV 45-Related HPV 52-Related HPV 58-Related										
				0.1	6,412	101	20,872.3	0.5		
				0.2	5,983	356	19,019.7	1.9		
				0.1	6,040	218	19,457.9	1.1		

† 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 in the PP population, and 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 .

Assessor's comment: 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 results are driven by HPV type, 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. 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.

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. 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 11-10 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 PP population.

Table 11-10 Impact of 9vHPV Vaccine on the Incidence of HPV 6/11/16/18-Related Cervical, Vulvar, and Vaginal Disease (Per-Protocol Efficacy Analysis Population)

Endpoint	9vHPV Vaccine (N=7,099)				qHPV Vaccine (N=7,105)				Risk Reduction [†] (%)	95% CI
	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		
HPV 6/11/16/18-Related Cervical, Vulvar, and Vaginal Disease					5,898	7	18,631.7	0.0		
Cervical Disease					5,832	3	17,123.4	0.0		
CIN 1					5,832	2	17,123.4	0.0		
CIN 2 or worse					5,832	1	17,127.2	0.0		
Vulvar and Vaginal Disease					5,893	4	18,615.3	0.0		
Condyloma					5,893	1	18,618.7	0.0		
VIN 1 or VaIN 1					5,893	2	18,618.6	0.0		
VIN 2/3 or VaIN 2/3 or worse					5,893	2	18,617.7	0.0		
HPV 6/11-Related Cervical, Vulvar, and Vaginal Disease					4,809	1	15,177.6	0.0		
Cervical Disease					4,759	1	13,976.2	0.0		
CIN 1					4,759	0	13,976.2	0.0		
CIN 2 or worse					4,759	1	13,976.2	0.0		
Vulvar and Vaginal Disease					4,805	0	15,161.0	0.0		
Condyloma					4,805	0	15,161.0	0.0		
Vulvar and Vaginal Disease					4,805	0	15,161.0	0.0		
Condyloma					4,805	0	15,161.0	0.0		
VIN 1 or VaIN 1					4,805	0	15,161.0	0.0		
VIN 2/3 or VaIN 2/3 or worse					4,805	0	15,161.0	0.0		
HPV 16/18-Related Cervical, Vulvar, and Vaginal Disease					5,792	6	18,302.4	0.0		
Cervical Disease					5,732	2	16,850.8	0.0		
CIN 1					5,732	2	16,850.8	0.0		
CIN 2 or worse					5,732	0	16,854.6	0.0		
Vulvar and Vaginal Disease					5,789	4	18,284.6	0.0		
Condyloma					5,789	1	18,288.0	0.0		
VIN 1 or VaIN 1					5,789	2	18,287.9	0.0		
VIN 2/3 or VaIN 2/3 or worse					5,789	2	18,287.0	0.0		
HPV 16-Related Cervical, Vulvar, and Vaginal Disease					4,871	6	15,396.4	0.0		
Cervical Disease					4,844	2	14,311.8	0.0		
CIN 1					4,844	2	14,311.8	0.0		
CIN 2 or worse					4,844	0	14,315.6	0.0		
Vulvar and Vaginal Disease					4,868	4	15,381.1	0.0		
Condyloma					4,868	1	15,384.6	0.0		
VIN 1 or VaIN 1					4,868	2	15,384.5	0.0		
VIN 2/3 or VaIN 2/3 or worse					4,868	2	15,383.6	0.0		
HPV 18-Related Cervical, Vulvar, and Vaginal Disease					5,478	0	17,321.5	0.0		
Cervical Disease					5,420	0	15,955.4	0.0		
CIN 1					5,420	0	15,955.4	0.0		
CIN 2 or worse					5,420	0	15,955.4	0.0		
Vulvar and Vaginal Disease					5,475	0	17,300.6	0.0		
Condyloma					5,475	0	17,300.6	0.0		
VIN 1 or VaIN 1					5,475	0	17,300.6	0.0		
VIN 2/3 or VaIN 2/3 or worse					5,475	0	17,300.6	0.0		

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

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 11-11 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 HITS population.

Table 11-11 Impact of 9vHPV Vaccine on the Incidence of HPV 6/11/16/18-Related Cervical, Vulvar, and Vaginal Disease (HPV-Naive Type-Specific Analysis Population)

Endpoint	9vHPV Vaccine (N=7,099)				qHPV Vaccine (N=7,105)				Risk Reduction [†] (%)	95% CI
	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		
HPV 6/11/16/18-Related Cervical, Vulvar, and Vaginal Disease					6,738	17	24,259.9	0.1		
Cervical Disease					6,599	9	22,500.7	0.0		
CIN 1					6,599	5	22,504.9	0.0		
CIN 2 or worse					6,599	5	22,508.0	0.0		
Vulvar and Vaginal Disease					6,737	9	24,255.7	0.0		
Condyloma					6,737	5	24,259.9	0.0		
VIN 1 or VaIN 1					6,737	3	24,265.5	0.0		
VIN 2/3 or VaIN 2/3 or worse					6,737	3	24,265.7	0.0		
HPV 6/11-Related Cervical, Vulvar, and Vaginal Disease					5,510	7	19,862.1	0.0		
Cervical Disease					5,398	4	18,469.9	0.0		
CIN 1					5,398	3	18,469.9	0.0		
CIN 2 or worse					5,398	2	18,473.4	0.0		
Vulvar and Vaginal Disease					5,509	4	19,849.8	0.0		
Condyloma					5,509	4	19,849.8	0.0		
VIN 1 or VaIN 1					5,509	1	19,855.6	0.0		
VIN 2/3 or VaIN 2/3 or worse					5,509	0	19,857.4	0.0		
HPV 6-Related Cervical, Vulvar, and Vaginal Disease					5,510	6	19,865.0	0.0		
Cervical Disease					5,398	4	18,469.9	0.0		
CIN 1					5,398	3	18,469.9	0.0		
CIN 2 or worse					5,398	2	18,473.4	0.0		
Vulvar and Vaginal Disease					5,509	3	19,852.7	0.0		
Condyloma					5,509	3	19,852.7	0.0		
VIN 1 or VaIN 1					5,509	0	19,857.4	0.0		
VIN 2/3 or VaIN 2/3 or worse					5,509	0	19,857.4	0.0		
HPV 11-Related Cervical, Vulvar, and Vaginal Disease					5,510	1	19,876.0	0.0		
Cervical Disease					5,398	0	18,473.4	0.0		
CIN 1					5,398	0	18,473.4	0.0		
CIN 2 or worse					5,398	0	18,473.4	0.0		
Vulvar and Vaginal Disease					5,509	1	19,854.5	0.0		
Condyloma					5,509	1	19,854.5	0.0		
VIN 1 or VaIN 1					5,509	1	19,855.6	0.0		
VIN 2/3 or VaIN 2/3 or worse					5,509	0	19,857.4	0.0		
HPV 16/18-Related Cervical, Vulvar, and Vaginal Disease					6,619	11	23,857.8	0.0		
Cervical Disease					6,482	6	22,154.3	0.0		
CIN 1					6,482	3	22,158.6	0.0		
CIN 2 or worse					6,482	4	22,158.1	0.0		
Vulvar and Vaginal Disease					6,618	6	23,845.3	0.0		
Condyloma					6,618	2	23,849.5	0.0		
VIN 1 or VaIN 1					6,618	2	23,850.0	0.0		
VIN 2/3 or VaIN 2/3 or worse					6,618	3	23,848.3	0.0		
HPV 16-Related Cervical, Vulvar, and Vaginal Disease					5,626	10	20,286.9	0.0		
Cervical Disease					5,510	5	19,014.7	0.0		
CIN 1					5,510	3	19,015.2	0.0		
CIN 2 or worse					5,510	3	19,018.5	0.0		
Vulvar and Vaginal Disease					5,625	6	20,273.2	0.0		
Condyloma					5,625	2	20,277.4	0.0		
VIN 1 or VaIN 1					5,625	2	20,277.9	0.0		
VIN 2/3 or VaIN 2/3 or worse					5,625	3	20,276.2	0.0		
HPV 18-Related Cervical, Vulvar, and Vaginal Disease					6,253	1	22,574.2	0.0		
Cervical Disease					6,125	1	20,967.8	0.0		
CIN 1					6,125	0	20,971.6	0.0		
CIN 2 or worse					6,125	1	20,967.8	0.0		
Vulvar and Vaginal Disease					6,252	0	22,553.9	0.0		
Condyloma					6,252	0	22,553.9	0.0		
VIN 1 or VaIN 1					6,252	0	22,553.9	0.0		
VIN 2/3 or VaIN 2/3 or worse					6,252	0	22,553.9	0.0		
[†] Percent reduction in the qHPV vaccine group incidence that was observed in the 9vHPV vaccine group, computed as 100x(1 - (9vHPV incidence/qHPV incidence)). 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 11-12 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 11-12. Impact of 9vHPV Vaccine on the Incidence of HPV 6/11/16/18-Related Persistent Infection (PPE and HN-TS Analysis Populations)

Analysis Population Endpoint	9vHPV Vaccine (N=7,099)				qHPV Vaccine (N=7,105)				Risk Reduction [†] (%)	95% CI
	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		
Per-Protocol Efficacy (PPE)										
Persistent Infection ≥6 Months [‡]										
HPV 6/11/16/18-Related					5,830	80	16,151.4	0.5		
HPV 6/11-Related					4,757	7	13,278.5	0.1		
HPV 6-Related					4,757	7	13,278.5	0.1		
HPV 11-Related					4,755	0	13,280.5	0.0		
HPV 16/18-Related					5,729	73	15,893.8	0.5		
HPV 16-Related					4,841	64	13,488.9	0.5		
HPV 18-Related					5,416	9	15,145.8	0.1		
Persistent Infection ≥12 Months [‡]										
HPV 6/11/16/18-Related					5,830	32	16,219.6	0.2		
HPV 6/11-Related					4,757	1	13,284.4	0.0		
HPV 6-Related					4,757	1	13,284.4	0.0		
HPV 11-Related					4,755	0	13,280.5	0.0		
HPV 16/18-Related					5,729	31	15,956.0	0.2		
HPV 16-Related					4,841	24	13,549.7	0.2		
HPV 18-Related					5,416	7	15,147.2	0.0		
HPV-Naïve Type-Specific (HN-TS)										
Persistent Infection ≥6 Months [‡]										
HPV 6/11/16/18-Related					6,582	180	21,218.1	0.8		
HPV 6/11-Related					5,385	32	17,640.5	0.2		
HPV 6-Related					5,385	29	17,647.3	0.2		
HPV 11-Related					5,385	3	7,706.2	0.0		
HPV 16/18-Related					6,465	149	20,046.2	0.7		
HPV 16-Related					5,495	111	18,005.3	0.7		
HPV 18-Related					6,109	32	20,030.4	0.2		
Persistent Infection ≥12 Months [‡]										
HPV 6/11/16/18-Related					6,582	102	21,357.6	0.5		
HPV 6/11-Related					5,385	20	17,659.8	0.1		
HPV 6-Related					5,385	18	17,665.1	0.1		
HPV 11-Related					5,385	2	17,701.9	0.0		
HPV 16/18-Related					6,465	83	21,066.5	0.4		
HPV 16-Related					5,495	60	18,108.9	0.3		
HPV 18-Related					6,109	23	20,047.3	0.1		

[†] 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).

Assessor's comment: The number of cases of the clinical endpoints related to HPV6/11/16/18 in the PP population was low, as expected. In the qvHPV 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 HN-TS 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.

Safety results

Dose-Ranging Substudy: Administration of the 9vHPV vaccine was generally well tolerated. The frequencies of clinical adverse experiences were generally comparable among the three 9vHPV vaccine groups and the qHPV vaccine group. .

Efficacy Substudy: Administration of the 9vHPV vaccine was generally well tolerated. The frequencies of clinical adverse experiences were generally comparable among the 2 vaccination groups (9vHPV vaccine group and qHPV vaccine group). Frequency of injection-site adverse experiences was higher in the 9vHPV vaccine group than in the qHPV vaccine group. subjects discontinued from the study due to a vaccine-related adverse experience⁴ in the qHPV vaccine group vaccine-related serious adverse experiences² in the qHPV vaccine group adverse experiences resulting in death⁵ in the qHPV vaccine group); none of these events were considered vaccine-related by the reporting investigator.

Adverse Event Summary (Vaccination and Follow-up Periods, Day 1 to Month 7) (All Vaccinated Subjects, Dose-Ranging Substudy)

	Low-Dose 9vHPV Vaccine n (%)	Mid-Dose 9vHPV Vaccine n (%)	High-Dose 9vHPV Vaccine n (%)	qHPV Vaccine n (%)
Subjects in population with follow-up				307
with one or more adverse events				278 (90.3)
injection-site				258 (83.8)
non-injection-site				165 (53.6)
with no adverse event				30 (9.7)
with vaccine-related [†] adverse events				268 (87.0)
injection-site				258 (83.8)
non-injection-site				90 (29.2)
with serious adverse events				8 (2.6)
with serious vaccine-related adverse events				0 (0.0)
who died				0 (0.0)
discontinued [‡] due to an adverse event				0 (0.0)
discontinued due to a vaccine-related adverse event				0 (0.0)
discontinued due to a serious adverse event				0 (0.0)
discontinued due to a serious vaccine-related adverse event				0 (0.0)
[†] Determined by the investigator to be related to the vaccine.				
[‡] Study medication withdrawn.				

Adverse Event Summary (Vaccination and Follow-up Periods, Day 1 through Visit Cut-Off Date) (All Vaccinated Subjects, Efficacy Substudy)

	9vHPV Vaccine n (%)	qHPV Vaccine n (%)
Subjects in population with follow-up with one or more adverse events		7,078
injection-site		6,444 (91.0)
non-injection-site		6,024 (85.1)
with no adverse event		3,957 (55.9)
with vaccine-related [†] adverse events		634 (9.0)
injection-site		6,202 (87.6)
non-injection-site		6,024 (85.1)
with serious adverse events		1,930 (27.3)
with serious vaccine-related adverse events		183 (2.6)
who died		5 (0.0)
discontinued [‡] due to an adverse event		5 (0.1)
discontinued due to a vaccine-related adverse event		4 (0.1)
discontinued due to a serious adverse event		3 (0.0)
discontinued due to a serious vaccine-related adverse event		1 (0.0)
		0 (0.0)
[†] Determined by the investigator to be related to the vaccine.		
[‡] Study medication withdrawn.		

Assessor's comment: The safety data from this study are in agreement with previously presented results for Gardasil, and no new safety issues were seen.

2.3.3. Discussion on clinical aspects

Gardasil was used as comparator in this study with the primary aim to evaluate the new. The results with respect to are being assessed in the assessment of the MAA for Gardasil, and will not be repeated here. The results for Gardasil were well in agreement with previously reported results, and the benefit risk balance for Gardasil is not changed by these results.

3. Rapporteur's overall conclusion and recommendation

Overall conclusion

The efficacy, immunogenicity and safety results of the current study relating to Gardasil are in agreement with previously presented results, and the benefit risk balance for Gardasil is not changed. No further regulatory action is required.

Recommendation

☒ **Fulfilled:**

No regulatory action required.

☐ **Not fulfilled:**

Additional clarifications requested

Not applicable.

Medicinal product no longer authorised