EMA/CHMP/767725/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: Gardasil 9

International non-proprietary name: human papillomavirus vaccine [types 6, 11, 16, 18, 31, 33, 45, 52, 58] (recombinant, adsorbed)

Procedure No. EMEA/H/C/003852/II/0053

Note

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

Status of this report and steps taken for the assessment			
Current step[1]	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	20 Dec 2021	20 Dec 2021
☐	CHMP Rapporteur Assessment Report	24 Jan 2022	19 Jan 2022
☐	CHMP members comments	07 Feb 2022	07 Feb 2022
☐	Updated CHMP Rapporteur Assessment Report	10 Feb 2022	n/a
☐	Start of written procedure	15 Feb 2022	15 Feb 2022
	Request for Supplementary Information	17 Feb 2022	17 Feb 2022
☐	Submission of Responses	22 Feb 2022	22 Feb 2022
☐	Re-start of procedure	23 Feb 2022	23 Feb 2022
☐	CHMP Rapporteur Assessment Report	09 Mar 2022	08 Mar 2022
☐	CHMP members comments	14 Mar 2022	n/a
☐	Updated CHMP Rapporteur Assessment Report	17 Mar 2022	n/a
☐	Start of written procedure	n/a	n/a
☒	Opinion	24 Mar 2022	24 Mar 2022

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, MSD Vaccines submitted to the European Medicines Agency on 3 December 2021 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

Update of section 5.1 of the SmPC in order to update long-term effectiveness and immunogenicity data following the final results of the Gardasil 9 long-term follow-up (LTFU) study V503-002-20 listed as a category 3 study in the RMP. In addition, the MAH took the opportunity to make some minor editorial changes (spacings) and included the updated long-term follow-up data received for the qHPV vaccine following V501-167 extension study. The Package Leaflet is updated accordingly.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

2. Overall conclusion and impact on the benefit/risk balance

The 9-valent vaccine Gardasil 9 (9vHPV) was authorised in EU in 2015.

Based on new data accrued from the now completed clinical study **V503-002-20**, the MAH proposed to update the SmPC section 5.1 by updating the information on effectiveness data for 9vHPV vaccines. Study **V503-002-20** had been assessed previously in separate worksharing procedures. The submission of the final study report is also in accordance with Article 46 of Regulation (EC) No 1901/2006 which sets out the obligation for MAHs to submit any MAH-sponsored studies involving the use of an authorised medicinal products in the paediatric population to the competent authority.

LTFU data for the quadrivalent vaccine, 10 years follow-up, from **V501-167** extension study, was assessed during a previous procedure for the tetravalent qHPV Gardasil (EMEA/H/C/000703/II/0087) and the changes were agreed with, but the data were not completely updated in the SmPC. In the current SmPC, information on **V501-167** is updated according to earlier agreement and therefore will not be repeated again in this procedure.

The phase 3 studies of the qHPV (Gardasil) and 9vHPV (Gardasil 9) vaccine programs were extended to provide LTFU data on effectiveness, immunogenicity, and safety. Subjects in the qHPV vaccine arm (control arm) of the pivotal 9vHPV vaccine efficacy study were offered vaccination with 9vHPV vaccine at the end of the base study. Because there is no control group in these LTFU studies, vaccine efficacy cannot be measured. In lieu of efficacy measurements, effectiveness of vaccination with the qHPV or 9vHPV vaccine is assessed. LTFU for effectiveness was collected using the system of registries and tissue repositories in Scandinavia. Effectiveness is measured in terms of the observed incidence rates of disease in comparison with the expected incidence in an unvaccinated population.

The final study report for Study V503-002-20 provides reassuring and consistent data on long-term effectiveness and immunogenicity or persistence of antibodies. The results speak for uniform long-term protection against infection and clinical disease caused by HPV types in the vaccine. The immune responses are rapid, substantial and well sustained, with current follow-up reaching up to 10 (9vHPV) years. Over time, GMT levels and seropositivity rates decline through an expected natural course and also number of persistent infections had been grown somewhat from 8 years follow-up to 10 years follow-up.

As there were no break-through cases of dysplasia so far, one can conclude that the protective effect of Gardasil 9 lasts at least 10 years.

The updated safety follow-up did not reveal any new safety concern.

The updates in SmPC are considered relevant, but the MAH was asked to describe also the incidence of the persistent HPV infections as it was a key effectiveness endpoint of the study and as no cases would be expected in the study cohort due to the limited sample size. The MAH updated the SmPC with information about incidence of the persistent HPV infections as requested.

The benefit-risk balance of Gardasil 9 remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation approved		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

Update of section 5.1 of the SmPC in order to update long-term effectiveness and immunogenicity data following the final results of the Gardasil 9 long-term follow-up (LTFU) paediatric study V503-002-20, listed as a category 3 study in the RMP. V503-002-20 is a LTFU extension of Study V503-002 (base study: a 3-year immunogenicity study of the 9vHPV vaccine in girls and boys 9 to 15 years of age, which assessed the immunogenicity and effectiveness of the 9vHPV vaccine through 10 years post dose 3. In addition, the MAH took the opportunity to make some minor editorial changes (spacings) and included the updated long term follow-up data already approved for the qHPV vaccine following V501-167 extension study. The details of local representatives for the MAH in the Package Leaflet is also updated.

☒is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB are recommended.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion EMEA/H/C/003852/II/0053

For more information, please refer to the Summary of Product Characteristics.

Annex: Rapporteur’s assessment comments on the type II variation

5. Introduction

The 9vHPV (Types 6, 11, 16, 18, 31, 33, 45, 52, 58) recombinant vaccine (GARDASIL™9), is an aluminum-adjuvanted recombinant VLP vaccine indicated for the prevention of cancer, dysplasia, genital warts, and infection caused by HPV types that are targeted by the vaccine in individuals from the age of 9 years.

This application is in support of an update to the SmPC and includes updated results from a clinical study of the 9vHPV vaccine program.

Pivotal Phase 3 studies from the 9vHPV vaccine program were extended to evaluate the long-term effectiveness and immunogenicity of the 9vHPV and qHPV vaccines in support of approved indications specified in the SmPC. The proposed variation aims to update section 5.1 of the Summary of Product Characteristics (SmPC)

Current type II variation:

1) Addition of long-term effectiveness and immunogenicity data from Gardasil 9 study V503-002-20 (MEA 010).

V503-002-20 is a LTFU extension of Study V503-002 (base study; a 3-year immunogenicity study of the 9vHPV vaccine in girls and boys 9 to 15 years of age, which assessed the immunogenicity and effectiveness of the 9vHPV vaccine through 10 years post dose 3.

A total of 1272 participants (971 female and 301 male participants) who received 3 doses of 9vHPV vaccine in the base study were followed in the study extension. Serum was collected in the extension at Months 66, 90, and 126 to evaluate persistence of the HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 antibody responses. LTFU for effectiveness was collected at study visits every 6 months during the study extension, starting when the participant reached 16 years of age. Three analyses were conducted, including 2 interim analyses (at Months 72 and 96, representing 5.5 years and 7.5 years post dose 3, respectively) and 1 final analysis (at Month 126, representing 10 years post dose 3). This application provides the final analyses for the study extension summarized in the CSR

6. Clinical Efficacy aspects

6.1. Methods – analysis of data submitted

Clinical Immunogenicity Endpoints

The immunogenicity endpoints for the LTFU study were the assessment of serum anti-HPV antibody levels (GMTs) and the proportions of participants who remained seropositive to vaccine HPV types at specific time points of the follow-up period to allow determination of the persistence of immune responses.

The primary immunoassay was HPV-9 cLIA. The IgG LIA, which is slightly more sensitive than the HPV-9 cLIA, was used as a secondary assay in supportive analyses to assess antibody persistence.

The immunogenicity analyses were conducted in the PPI population, consisting of individuals who received all 3 doses of vaccinations with the correct dose of the correct clinical material and within acceptable day ranges, provided a Month 7 serology result within 21 to 49 days post dose 3, were seronegative by cLIA to the appropriate HPV type at Day 1 (For HPV 6 and 11, participants must have been seronegative to both HPV 6 and 11 at Day 1), and had no other protocol violations that could have interfered with the evaluation of participant's immune response to the study vaccine.

Clinical Effectiveness Endpoints

The key effectiveness endpoints for the study are described in Table 1.

Table 1. Key Effectiveness Endpoints for 9vHPV Vaccine Long-Term Follow-up Study.

Study	Key Effectiveness Endpoints*	Definition
V503-002-20	*(Females only)*: HPV6/11/16/18/31/33/45/52/58-related 6-month persistent infection, CIN, AIS, VIN, VaIN, genital warts and cervical/vaginal/vulvar cancer *(Males only)*: HPV6/11/16/18/31/33/45/52/58-related 6-month persistent infection, PIN, genital warts, and penile/perineal/perianal cancer	An endpoint of 6-month persistent infection was positive for the same HPV type by the more consecutive cervico-vaginal/external genital consecutive visits 6 months (±1 month) apart or An endpoint of HPV6/11/16/18/31/33/45/52/58-cervical/vaginal/vulvar cancer was defined if both 33, 45, 52, or 58 DNA was detected in biopsy the Pathology Panel was CIN, AIS, VIN, VaIN, An endpoint of HPV6/11/16/18/31/33/45/52/58-cancer was defined if both of the following was detected in biopsy thin section by HPV PCR; PIN, genital warts, or penile/perineal/perianal cancer.
* Secondary effectiveness endpoints for V503-002-20 (because V503-002-20 has no primary effectiveness endpoints). AIS: adenocarcinoma in situ; CIN: cervical intraepithelial neoplasia; CIN1: CIN Grade 1; CIN2: CIN Grade 2; CIN3: CIN Grade 3; PIN: penile intraepithelial neoplasia; PCR: polymerase chain reaction; VaIN: vaginal intraepithelial neoplasia; VIN: vulvar intraepithelial neoplasia.		

For the determination of endpoints, tissue samples collected during the study were reviewed by an adjudication panel of 4 pathologists and tested by PCR to detect the presence of HPV deoxyribonucleic acid.

The primary effectiveness analyses were conducted in the PPE population consisting of individuals who received all 3 doses of vaccinations with the correct dose of the correct clinical material within 1 year, were seronegative by cLIA to the appropriate HPV type at Day 1 (seronegative to both HPV 6 and 11 in analysis of HPV 6- and 11-related endpoints), and had no other protocol violations that could have interfered with the evaluation of effectiveness of the study vaccine. Only PPE population-eligible participants who were at least 16 years of age and had at least 1 follow-up visit with PCR data contributed to the PPE analyses.

6.2. Results

Final Analysis of Protocol V503-002-20: Antibody Persistence in Girls and Boys 9 to 15 Years of Age Administered 9vHPV Vaccine

GMTs assessed by HPV-9 cLIA and IgG LIA to each of the 9 HPV types were highest at Month 7 (1 month postdose 3) and decreased thereafter. The steepest decline in GMTs occurred between Month 7 and Month 12, after which titers continued to gradually decrease through **Month 126** (10 years postdose 3). Seropositivity rates were >99% at Month 7 and remained high at Month 126 (≥81.3% and ≥94.9% measured by cLIA and IgG LIA, respectively) for each of the 9 HPV types.

In summary, the Month 126 immunogenicity results demonstrated persistent HPV antibody responses through 10 years postvaccination in girls and boys 9 to 15 years of age who received a 3-dose regimen of 9vHPV vaccine (Table 2 & 3).

Table 2. Summary of Anti-HPV cLIA Geometric Mean Titers by Age Group among Female and Male Participants (PIP[a]).

		9vHPV Vaccine								
		9 to 12 Years of Age at Enrollment (N=860)			13 to 15 Years of Age at Enrollment (N=412)			Total (N=1272)		
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	759	< 16	(<16, <16)	366	< 16	(<16, <16)	1,125	< 16	(<16, <16)
	Month 07	759	2,040.9	(1,917.2, 2,172.5)	366	1,312.5	(1,199.6, 1,436.1)	1,125	1,767.9	(1,677.1, 1,863.5)
	Month 12	349	710.5	(649.9, 776.8)	163	529.2	(464.5, 603.0)	512	646.9	(600.5, 697.0)
	Month 24	349	340.1	(310.4, 372.7)	163	270.9	(237.0, 309.8)	512	316.4	(293.2, 341.4)
	Month 36	345	260.0	(236.1, 286.2)	161	216.5	(188.0, 249.2)	506	245.2	(226.5, 265.6)
	Month 66	310	186.2	(167.6, 206.9)	132	145.5	(123.8, 170.9)	442	173.0	(158.3, 189.0)
	Month 90	288	147.0	(131.6, 164.1)	137	122.8	(104.6, 144.1)	425	138.7	(126.6, 151.9)
	Month 126	327	136.9	(124.0, 151.2)	190	106.2	(93.3, 121.0)	517	124.7	(115.2, 135.0)
Anti-HPV 11	Day 1	759	< 6	(<6, <6)	366	< 6	(<6, <6)	1,125	< 6	(<6, <6)
	Month 07	759	1,469.3	(1,380.0, 1,564.5)	366	1,008.0	(921.0, 1,103.3)	1,125	1,299.8	(1,233.3, 1,369.9)
	Month 12	351	453.3	(408.7, 502.7)	165	344.8	(296.5, 401.1)	516	415.3	(381.1, 452.6)
	Month 24	350	201.7	(181.0, 224.8)	164	161.8	(138.1, 189.6)	514	188.0	(171.8, 205.7)
	Month 36	349	151.7	(136.0, 169.2)	164	132.3	(112.8, 155.1)	513	145.2	(132.7, 158.9)
	Month 66	302	112.9	(100.7, 126.6)	128	93.1	(78.2, 111.0)	430	106.6	(96.9, 117.3)
	Month 90	279	97.1	(86.3, 109.3)	135	80.6	(68.0, 95.5)	414	91.4	(82.9, 100.7)
	Month 126	316	92.4	(83.2, 102.5)	185	70.8	(61.7, 81.1)	501	83.7	(77.0, 91.0)
Anti-HPV 16	Day 1	774	< 12	(<12, <12)	369	< 12	(<12, <12)	1,143	< 12	(<12, <12)
	Month 07	774	8,676.1	(8,191.9, 9,188.9)	369	5,632.4	(5,182.9, 6,120.9)	1,143	7,546.6	(7,188.1, 7,923.0)
	Month 12	358	2,997.5	(2,755.6, 3,260.7)	166	2,083.1	(1,840.9, 2,357.1)	524	2,671.1	(2,488.0, 2,867.6)
	Month 24	357	1,334.7	(1,209.1, 1,473.2)	165	916.8	(792.8, 1,060.1)	522	1,185.3	(1,090.9, 1,287.8)
	Month 36	356	989.0	(888.7, 1,100.7)	165	721.1	(616.3, 843.8)	521	894.8	(818.5, 978.4)
	Month 66	314	645.7	(574.1, 726.3)	130	496.1	(413.3, 595.6)	444	597.8	(541.2, 660.2)
	Month 90	289	531.2	(468.7, 602.0)	133	437.2	(363.6, 525.8)	422	499.6	(450.3, 554.2)
	Month 126	328	468.1	(416.1, 526.5)	183	316.4	(270.2, 370.3)	511	406.8	(369.7, 447.6)
Anti-HPV 18	Day 1	777	< 8	(<8, <8)	372	< 8	(<8, <8)	1,149	< 8	(<8, <8)
	Month 07	777	2,745.2	(2,563.6, 2,939.7)	372	1,561.3	(1,414.2, 1,723.6)	1,149	2,286.8	(2,157.3, 2,424.1)
	Month 12	358	732.6	(654.0, 820.6)	166	433.9	(367.3, 512.6)	524	620.6	(563.8, 683.1)
	Month 24	357	305.9	(272.1, 343.9)	165	175.8	(148.0, 208.8)	522	256.7	(232.5, 283.5)
	Month 36	356	229.9	(203.3, 259.9)	165	139.9	(116.9, 167.5)	521	196.4	(177.2, 217.8)
	Month 66	318	176.2	(159.2, 194.9)	132	137.9	(117.9, 161.3)	450	164.0	(150.5, 178.6)
	Month 90	295	163.8	(146.7, 182.8)	135	140.4	(119.4, 165.1)	430	156.0	(142.5, 170.9)
	Month 126	333	150.9	(137.3, 165.8)	192	110.6	(97.7, 125.2)	525	134.7	(124.8, 145.3)
Anti-HPV 31	Day 1	771	< 4	(<4, <4)	365	< 4	(<4, <4)	1,136	< 4	(<4, <4)
	Month 07	771	2,360.3	(2,212.3, 2,518.3)	365	1,432.4	(1,303.7, 1,573.8)	1,136	2,010.4	(1,902.7, 2,124.2)
	Month 12	358	749.6	(674.3, 833.3)	166	436.4	(373.6, 509.8)	524	631.5	(577.1, 691.0)
	Month 24	357	332.1	(295.3, 373.4)	165	186.9	(157.3, 222.1)	522	276.9	(250.7, 305.9)
	Month 36	356	268.4	(239.0, 301.5)	165	167.3	(141.1, 198.3)	521	231.1	(209.6, 254.8)
	Month 66	318	181.0	(161.2, 203.3)	131	116.2	(97.0, 139.2)	449	159.0	(144.0, 175.6)
	Month 90	295	149.4	(132.8, 167.9)	135	103.4	(87.0, 123.0)	430	133.1	(120.6, 146.8)
	Month 126	333	136.1	(122.3, 151.6)	187	85.8	(74.3, 99.0)	520	115.3	(105.6, 125.9)
Anti-HPV 33	Day 1	772	< 4	(<4, <4)	374	< 4	(<4, <4)	1,146	< 4	(<4, <4)
	Month 07	772	1,148.2	(1,082.0, 1,218.4)	374	750.6	(689.2, 817.4)	1,146	999.4	(950.7, 1,050.7)
	Month 12	353	366.7	(331.8, 405.2)	168	241.2	(208.7, 278.8)	521	320.4	(294.6, 348.4)
	Month 24	352	150.7	(134.6, 168.8)	167	101.8	(86.3, 120.0)	519	132.8	(120.8, 146.0)
	Month 36	351	114.2	(101.8, 128.1)	167	84.2	(71.2, 99.4)	518	103.5	(94.1, 113.8)
	Month 66	314	91.3	(82.0, 101.7)	134	69.9	(59.2, 82.5)	448	84.3	(77.0, 92.3)
	Month 90	293	76.1	(68.0, 85.1)	138	61.9	(52.6, 72.8)	431	71.2	(64.9, 78.1)
	Month 126	331	70.3	(63.7, 77.5)	191	51.1	(44.9, 58.1)	522	62.5	(57.8, 67.7)
Anti-HPV 45	Day 1	780	< 3	(<3, <3)	374	< 3	(<3, <3)	1,154	< 3	(<3, <3)
	Month 07	780	993.2	(923.3, 1,068.4)	374	560.2	(504.1, 622.4)	1,154	825.0	(775.4, 877.7)
	Month 12	359	286.9	(253.3, 324.9)	168	153.3	(127.8, 183.8)	527	234.9	(211.4, 261.1)
	Month 24	358	115.1	(100.7, 131.6)	167	58.8	(48.3, 71.6)	525	93.0	(83.0, 104.2)

	Month 36	357	87.1	(75.9, 99.9)	167	48.3	(39.5, 59.0)	524	72.1	(64.3, 81.0)
	Month 66	314	68.6	(60.8, 77.3)	127	42.5	(35.2, 51.3)	441	59.8	(53.9, 66.3)
	Month 90	285	60.8	(53.9, 68.5)	130	40.6	(34.0, 48.4)	415	53.6	(48.4, 59.2)
	Month 126	318	53.2	(47.7, 59.2)	176	32.5	(28.1, 37.6)	494	44.6	(40.8, 48.8)
Anti-HPV 52	Day 1	779	< 3	(<3, <3)	374	< 3	(<3, <3)	1,153	< 3	(<3, <3)
	Month 07	779	1,119.7	(1,051.9, 1,191.8)	374	729.1	(666.3, 797.8)	1,153	974.2	(924.3, 1,026.8)
	Month 12	360	339.3	(304.9, 377.6)	168	229.7	(196.4, 268.6)	528	299.7	(274.0, 327.8)
	Month 24	359	149.4	(134.2, 166.2)	167	103.9	(88.8, 121.5)	526	133.1	(121.7, 145.5)
	Month 36	358	113.3	(101.5, 126.4)	167	83.9	(71.4, 98.5)	525	102.9	(94.0, 112.8)
	Month 66	321	89.4	(80.3, 99.5)	134	68.7	(58.2, 81.1)	455	82.7	(75.5, 90.6)
	Month 90	297	71.3	(64.1, 79.4)	138	58.9	(50.3, 69.0)	435	67.1	(61.4, 73.4)
	Month 126	333	63.0	(57.3, 69.2)	191	47.3	(41.7, 53.6)	524	56.7	(52.6, 61.2)
Anti-HPV 58	Day 1	773	< 4	(<4, <4)	370	< 4	(<4, <4)	1,143	< 4	(<4, <4)
	Month 07	773	1,522.4	(1,432.9, 1,617.4)	370	980.8	(898.6, 1,070.6)	1,143	1,320.4	(1,254.5, 1,389.8)
	Month 12	356	541.9	(490.4, 598.9)	166	354.3	(306.1, 410.1)	522	473.4	(435.2, 515.0)
	Month 24	355	226.8	(203.0, 253.4)	165	144.5	(122.8, 170.0)	520	196.5	(179.0, 215.8)
	Month 36	354	173.6	(154.9, 194.6)	165	116.1	(98.2, 137.3)	519	152.8	(138.8, 168.1)
	Month 66	315	123.1	(109.5, 138.3)	132	81.4	(68.0, 97.5)	447	109.0	(98.6, 120.4)
	Month 90	289	105.2	(93.4, 118.5)	136	75.0	(63.1, 89.2)	425	94.4	(85.5, 104.2)
	Month 126	328	92.5	(83.5, 102.4)	189	64.4	(56.3, 73.6)	517	81.0	(74.6, 88.0)

[a] Includes all participants who (1) Received all 3 vaccinations with the correct dose of the correct clinical material within acceptable day ranges, (2) Were seronegative by cLIA to the appropriate HPV type at Day 1, (3) Had a Month 7 serology result within an acceptable day range and (4) Had no other protocol violations that could interfere with the evaluation of participant's immune response to the study vaccine. Specifically, at base study Day 1, participants satisfied the inclusion criterion 5 (i.e., "Participant must not yet have had coitarche and does not plan on becoming sexually active during the Day 1 through Month 7 period.") specified in Section 2.2 of the protocol of the base study (i.e., Protocol V503-002-00). To be included in the PPI population for HPV 6 and 11, participants must have been seronegative by cLIA to both HPV 6 and 11 at Day 1. To be included in the PPI population for any other vaccine HPV type, participants needed to be seronegative by cLIA at Day 1 only for the HPV type being analyzed

N = Number of participants enrolled in Protocol V503-002-20.

n = Number of participants contributing to the analysis.

CI = Confidence interval; cLIA = Competitive Luminex immunoassay; GMT = Geometric mean titer; mMU = Milli Merck units; HPV = Human papillomavirus; 9vHPV = Nine-valent human papillomavirus (Types 6, 11, 16, 18, 31, 33, 45, 52, 58) Recombinant Vaccine

Table 3. Summary of Anti-HPV cLIA Seropositivity Rates by Age Group Among Female and Male Participants

		9vHPV Vaccine											
		9 to 12 Years of Age at Enrollment (N=860)				13 to 15 Years of Age at Enrollment (N=412)				Total (N=1272)			
				Seropositive				Seropositive				Seropositive	
Assay (cLIA)	Time Point	n	m	Percent	95% CI	n	m	Percent	95% CI	n	m	Percent	95% CI
Anti-HPV 6	Day 1	759	0	0.0	(0.0%, 0.5%)	366	0	0.0	(0.0%, 1.0%)	1,125	0	0.0	(0.0%, 0.3%)
	Month 07	759	758	99.9	(99.3%, 100%)	366	363	99.2	(97.6%, 99.8%)	1,125	1,121	99.6	(99.1%, 99.9%)
	Month 12	349	348	99.7	(98.4%, 100%)	163	163	100.0	(97.8%, 100%)	512	511	99.8	(98.9%, 100%)
	Month 24	349	346	99.1	(97.5%, 99.8%)	163	163	100.0	(97.8%, 100%)	512	509	99.4	(98.3%, 99.9%)
	Month 36	345	339	98.3	(96.3%, 99.4%)	161	160	99.4	(96.6%, 100%)	506	499	98.6	(97.2%, 99.4%)
	Month 66	310	279	90.0	(86.1%, 93.1%)	132	113	85.6	(78.4%, 91.1%)	442	392	88.7	(85.4%, 91.5%)
	Month 90	288	244	84.7	(80.0%, 88.7%)	137	117	85.4	(78.4%, 90.8%)	425	361	84.9	(81.2%, 88.2%)
	Month 126	327	277	84.7	(80.3%, 88.4%)	190	153	80.5	(74.2%, 85.9%)	517	430	83.2	(79.7%, 86.3%)
Anti-HPV 11	Day 1	759	0	0.0	(0.0%, 0.5%)	366	0	0.0	(0.0%, 1.0%)	1,125	0	0.0	(0.0%, 0.3%)
	Month 07	759	759	100.0	(99.5%, 100%)	366	366	100.0	(99.0%, 100%)	1,125	1,125	100.0	(99.7%, 100%)
	Month 12	351	351	100.0	(99.0%, 100%)	165	165	100.0	(97.8%, 100%)	516	516	100.0	(99.3%, 100%)
	Month 24	350	346	98.9	(97.1%, 99.7%)	164	164	100.0	(97.8%, 100%)	514	510	99.2	(98.0%, 99.8%)
	Month 36	349	345	98.9	(97.1%, 99.7%)	164	161	98.2	(94.7%, 99.6%)	513	506	98.6	(97.2%, 99.4%)
	Month 66	302	267	88.4	(84.3%, 91.8%)	128	113	88.3	(81.4%, 93.3%)	430	380	88.4	(85.0%, 91.2%)
	Month 90	279	244	87.5	(83.0%, 91.1%)	135	112	83.0	(75.5%, 88.9%)	414	356	86.0	(82.3%, 89.2%)
	Month 126	316	280	88.6	(84.6%, 91.9%)	185	150	81.1	(74.7%, 86.5%)	501	430	85.8	(82.5%, 88.8%)
Anti-HPV 16	Day 1	774	0	0.0	(0.0%, 0.5%)	369	0	0.0	(0.0%, 1.0%)	1,143	0	0.0	(0.0%, 0.3%)
	Month 07	774	774	100.0	(99.5%, 100%)	369	369	100.0	(99.0%, 100%)	1,143	1,143	100.0	(99.7%, 100%)
	Month 12	358	358	100.0	(99.0%, 100%)	166	166	100.0	(97.8%, 100%)	524	524	100.0	(99.3%, 100%)
	Month 24	357	357	100.0	(99.0%, 100%)	165	165	100.0	(97.8%, 100%)	522	522	100.0	(99.3%, 100%)
	Month 36	356	355	99.7	(98.4%, 100%)	165	165	100.0	(97.8%, 100%)	521	520	99.8	(98.9%, 100%)
	Month 66	314	314	100.0	(98.8%, 100%)	130	130	100.0	(97.2%, 100%)	444	444	100.0	(99.2%, 100%)
	Month 90	289	286	99.0	(97.0%, 99.8%)	133	131	98.5	(94.7%, 99.8%)	422	417	98.8	(97.3%, 99.6%)
	Month 126	328	322	98.2	(96.1%, 99.3%)	183	177	96.7	(93.0%, 98.8%)	511	499	97.7	(95.9%, 98.8%)
Anti-HPV 18	Day 1	777	0	0.0	(0.0%, 0.5%)	372	0	0.0	(0.0%, 1.0%)	1,149	0	0.0	(0.0%, 0.3%)
	Month 07	777	777	100.0	(99.5%, 100%)	372	372	100.0	(99.0%, 100%)	1,149	1,149	100.0	(99.7%, 100%)
	Month 12	358	357	99.7	(98.5%, 100%)	166	166	100.0	(97.8%, 100%)	524	523	99.8	(98.9%, 100%)
	Month 24	357	353	98.9	(97.2%, 99.7%)	165	159	96.4	(92.3%, 98.7%)	522	512	98.1	(96.5%, 99.1%)
	Month 36	356	347	97.5	(95.3%, 98.8%)	165	152	92.1	(86.9%, 95.7%)	521	499	95.8	(93.7%, 97.3%)
	Month 66	318	278	87.4	(83.3%, 90.9%)	132	104	78.8	(70.8%, 85.4%)	450	382	84.9	(81.2%, 88.1%)

	Month 90	295	252	85.4	(80.9%, 89.2%)	135	111	82.2	(74.7%, 88.3%)	430	363	84.4	(80.6%, 87.7%)
	Month 126	333	281	84.4	(80.0%, 88.1%)	192	146	76.0	(69.4%, 81.9%)	525	427	81.3	(77.7%, 84.6%)
Anti-HPV 31	Day 1	771	0	0.0	(0.0%, 0.5%)	365	0	0.0	(0.0%, 1.0%)	1,136	0	0.0	(0.0%, 0.3%)
	Month 07	771	771	100.0	(99.5%, 100%)	365	365	100.0	(99.0%, 100%)	1,136	1,136	100.0	(99.7%, 100%)
	Month 12	358	358	100.0	(99.0%, 100%)	166	166	100.0	(97.8%, 100%)	524	524	100.0	(99.3%, 100%)
	Month 24	357	356	99.7	(98.4%, 100%)	165	163	98.8	(95.7%, 99.9%)	522	519	99.4	(98.3%, 99.9%)
	Month 36	356	354	99.4	(98.0%, 99.9%)	165	162	98.2	(94.8%, 99.6%)	521	516	99.0	(97.8%, 99.7%)
	Month 66	318	303	95.3	(92.3%, 97.3%)	131	118	90.1	(83.6%, 94.6%)	449	421	93.8	(91.1%, 95.8%)
	Month 90	295	278	94.2	(90.9%, 96.6%)	135	118	87.4	(80.6%, 92.5%)	430	396	92.1	(89.1%, 94.5%)
	Month 126	333	315	94.6	(91.6%, 96.8%)	187	158	84.5	(78.5%, 89.4%)	520	473	91.0	(88.2%, 93.3%)
Anti-HPV 33	Day 1	772	0	0.0	(0.0%, 0.5%)	374	0	0.0	(0.0%, 1.0%)	1,146	0	0.0	(0.0%, 0.3%)
	Month 07	772	772	100.0	(99.5%, 100%)	374	374	100.0	(99.0%, 100%)	1,146	1,146	100.0	(99.7%, 100%)
	Month 12	353	353	100.0	(99.0%, 100%)	168	168	100.0	(97.8%, 100%)	521	521	100.0	(99.3%, 100%)
	Month 24	352	350	99.4	(98.0%, 99.9%)	167	167	100.0	(97.8%, 100%)	519	517	99.6	(98.6%, 100%)
	Month 36	351	345	98.3	(96.3%, 99.4%)	167	165	98.8	(95.7%, 99.9%)	518	510	98.5	(97.0%, 99.3%)
	Month 66	314	291	92.7	(89.2%, 95.3%)	134	118	88.1	(81.3%, 93.0%)	448	409	91.3	(88.3%, 93.7%)
	Month 90	293	264	90.1	(86.1%, 93.3%)	138	119	86.2	(79.3%, 91.5%)	431	383	88.9	(85.5%, 91.7%)
	Month 126	331	300	90.6	(87.0%, 93.5%)	191	152	79.6	(73.2%, 85.1%)	522	452	86.6	(83.4%, 89.4%)
Anti-HPV 45	Day 1	780	0	0.0	(0.0%, 0.5%)	374	0	0.0	(0.0%, 1.0%)	1,154	0	0.0	(0.0%, 0.3%)
	Month 07	780	780	100.0	(99.5%, 100%)	374	373	99.7	(98.5%, 100%)	1,154	1,153	99.9	(99.5%, 100%)
	Month 12	359	358	99.7	(98.5%, 100%)	168	167	99.4	(96.7%, 100%)	527	525	99.6	(98.6%, 100%)
	Month 24	358	350	97.8	(95.6%, 99.0%)	167	153	91.6	(86.3%, 95.3%)	525	503	95.8	(93.7%, 97.4%)
	Month 36	357	346	96.9	(94.6%, 98.5%)	167	146	87.4	(81.4%, 92.0%)	524	492	93.9	(91.5%, 95.8%)
	Month 66	314	287	91.4	(87.7%, 94.3%)	127	103	81.1	(73.2%, 87.5%)	441	390	88.4	(85.1%, 91.3%)
	Month 90	285	262	91.9	(88.1%, 94.8%)	130	109	83.8	(76.4%, 89.7%)	415	371	89.4	(86.0%, 92.2%)
	Month 126	318	288	90.6	(86.8%, 93.5%)	176	134	76.1	(69.1%, 82.2%)	494	422	85.4	(82.0%, 88.4%)
Anti-HPV 52	Day 1	779	0	0.0	(0.0%, 0.5%)	374	0	0.0	(0.0%, 1.0%)	1,153	0	0.0	(0.0%, 0.3%)
	Month 07	779	779	100.0	(99.5%, 100%)	374	374	100.0	(99.0%, 100%)	1,153	1,153	100.0	(99.7%, 100%)
	Month 12	360	360	100.0	(99.0%, 100%)	168	168	100.0	(97.8%, 100%)	528	528	100.0	(99.3%, 100%)
	Month 24	359	359	100.0	(99.0%, 100%)	167	164	98.2	(94.8%, 99.6%)	526	523	99.4	(98.3%, 99.9%)
	Month 36	358	354	98.9	(97.2%, 99.7%)	167	164	98.2	(94.8%, 99.6%)	525	518	98.7	(97.3%, 99.5%)
	Month 66	321	298	92.8	(89.4%, 95.4%)	134	122	91.0	(84.9%, 95.3%)	455	420	92.3	(89.5%, 94.6%)
	Month 90	297	272	91.6	(87.8%, 94.5%)	138	123	89.1	(82.7%, 93.8%)	435	395	90.8	(87.7%, 93.3%)
	Month 126	333	306	91.9	(88.4%, 94.6%)	191	158	82.7	(76.6%, 87.8%)	524	464	88.5	(85.5%, 91.1%)
Anti-HPV 58	Day 1	773	0	0.0	(0.0%, 0.5%)	370	0	0.0	(0.0%, 1.0%)	1,143	0	0.0	(0.0%, 0.3%)
	Month 07	773	773	100.0	(99.5%, 100%)	370	370	100.0	(99.0%, 100%)	1,143	1,143	100.0	(99.7%, 100%)
	Month 12	356	356	100.0	(99.0%, 100%)	166	166	100.0	(97.8%, 100%)	522	522	100.0	(99.3%, 100%)
	Month 24	355	354	99.7	(98.4%, 100%)	165	165	100.0	(97.8%, 100%)	520	519	99.8	(98.9%, 100%)
	Month 36	354	352	99.4	(98.0%, 99.9%)	165	162	98.2	(94.8%, 99.6%)	519	514	99.0	(97.8%, 99.7%)
	Month 66	315	306	97.1	(94.6%, 98.7%)	132	127	96.2	(91.4%, 98.8%)	447	433	96.9	(94.8%, 98.3%)
	Month 90	289	281	97.2	(94.6%, 98.8%)	136	134	98.5	(94.8%, 99.8%)	425	415	97.6	(95.7%, 98.9%)
	Month 126	328	317	96.6	(94.1%, 98.3%)	189	183	96.8	(93.2%, 98.8%)	517	500	96.7	(94.8%, 98.1%)

[a] Includes all participants who (1) Received all 3 vaccinations with the correct dose of the correct clinical material within acceptable day ranges, (2) Were seronegative by cLIA to the appropriate HPV type at Day 1, (3) Had a Month 7 serology result within an acceptable day range, and (4) Had no other protocol violations that could interfere with the evaluation of participant's immune response to the study vaccine. Specifically, at base study Day 1, participants satisfied the inclusion criterion 5 (i.e., "Participant must not yet have had coitarche and does not plan on becoming sexually active during the Day
1 through Month 7 period.") specified in Section 2.2 of the protocol of the base study (i.e., Protocol V503-002-00). To be included in the PPI population for HPV 6 and 11, participants must have been seronegative by cLIA to both HPV 6 and 11 at Day 1. To be included in the PPI population for any other vaccine HPV type, participants needed to be seronegative by cLIA at Day 1 only for the HPV type
being analyzed.

Percent represents proportion of participants with anti-HPV serum levels ≥ 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.
For Month 66 and after; HPV serum levels ≥ 50, 29, 41, 59, 29, 22, 15, 20, and 15 mMU/mL for HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 respectively

N = Number of participants enrolled in Protocol V503-002-20.

n = Number of participants contributing to the analysis.

m = Number of seropositive participants.

CI = Confidence interval; cLIA = Competitive Luminex immunoassay;

Assessor´s comment: Over time, GMT levels and seropositivity rates declined through an expected natural course. After 10 years, the vaccine induced antibodies are still detectable among more than 80 % of participants, depending on HPV type. There has not been a remarkable drop of antibody level or seropositivity from month 90 to month 126 indicating that antibody level is rather stable between 8 to 10 years.

Final Analysis of Protocol V503-002-20: Long-term Clinical Effectiveness of 9vHPV Vaccine in Girls and Boys 9 to 15 Years of Age

Participants in the PPE population (n=1134) were followed for effectiveness for a maximum of 11.0 years (median: 10.0 years) postdose 3. Female participants (n=872) were followed for up to 11.0 years (median: 10.0 years) postdose 3; male participants (n=262) were followed for up to 10.6 years (median: 9.9 years) postdose 3.

One case of HPV 6/11/16/18/31/33/45/52/58-related low-grade cervical dysplasia was observed in female participants 9 to 15 years of age in the PPE population (866 participants, 4576.1 person-years follow-up). This case was diagnosed as CIN1, which was based on a CIN1 diagnosis associated with HPV

39 and HPV 59 on a cervical biopsy and a CIN1 diagnosis associated with HPV 16, HPV 39 and HPV 59 on an endocervical curettage. Cervical biopsy was positive for HPV 39 and HPV 59 with no pathological abnormalities. Persistent infection was observed with HPV 39 and HPV 59; HPV 16 was detected only once in association with the endocervical curettage. Based on these results, it is likely that the lesion was caused by HPV 39 or HPV 59. This CIN1 lesion is not considered a breakthrough since these 2 HPV types are not covered by the 9vHPV vaccine.

No (0) cases of HPV 6/11/16/18/31/33/45/52/58-related PIN, genital warts, or penile/perineal/perianal cancer were observed in boys 9 to 15 years of age in the PPE population (261 participants, 1278.6 person-years follow-up).

Incidence rates of HPV 6/11/16/18/31/33/45/52/58-related 6-month persistent infection in females and males were low (52.4 and 54.6 per 10000 person-years, respectively) and within ranges expected in vaccinated cohorts (based on results from previous efficacy studies of the 9vHPV and qHPV vaccines) (Table4).

Table 4. Incidence of HPV 6/11/16/18/31/33/45/52/58-Related Persistent Infection in Females and Males Who Received 9vHPV Vaccine (Per-Protocol Effectiveness Population)

	Females (N=971)				Males (N=301)			
Endpoint	n	Number of Cases	Person-Years Follow-up[a]	Incidence per 10,000 Person-Years Follow-up Estimate (95% CI)	n	Number of Cases	Person-Years Follow-up[a]	Incidence per 10,000 Person-Years Follow-up Estimate (95% CI)
HPV 6/11/16/18/31/33/45/52/58-Related Persistent Infection ≥6 Months[b]	872	24	4,579.6	52.4 (33.6, 78.0)	261	7	1,282.7	54.6 (21.9, 112.4)
By HPV Type								
HPV 6/11/16/18-related	870	22	4,580.4	48.0 (30.1, 72.7)	261	1	1,296.1	7.7 (0.2, 43.0)
HPV 6-related	847	4	4,520.4	8.8 (2.4, 22.7)	255	0	1,273.4	0.0 (0.0, 29.0)
HPV 11-related	847	0	4,530.1	0.0 (0.0, 8.1)	255	1	1,270.9	7.9 (0.2, 43.8)
HPV 16-related	860	17	4,541.3	37.4 (21.8, 59.9)	260	0	1,293.0	0.0 (0.0, 28.5)
HPV 18-related	867	1	4,627.2	2.2 (0.1, 12.0)	259	0	1,285.9	0.0 (0.0, 28.7)
HPV 31/33/45/52/58-related	872	2	4,649.5	4.3 (0.5, 15.5)	261	6	1,285.2	46.7 (17.1, 101.6)
HPV 31-related	855	0	4,567.1	0.0 (0.0, 8.1)	259	2	1,287.6	15.5 (1.9, 56.1)
HPV 33-related	866	1	4,625.7	2.2 (0.1, 12.0)	259	0	1,294.0	0.0 (0.0, 28.5)
HPV 45-related	871	0	4,652.5	0.0 (0.0, 7.9)	261	1	1,292.6	7.7 (0.2, 43.1)
HPV 52-related	870	0	4,645.5	0.0 (0.0, 7.9)	261	4	1,286.8	31.1 (8.5, 79.6)
HPV 58-related	863	1	4,611.5	2.2 (0.1, 12.1)	259	0	1,293.2	0.0 (0.0, 28.5)
HPV 6/11/16/18/31/33/45/52/58-Related Persistent Infection ≥12 Months[c]	872	9	4,621.1	19.5 (8.9, 37.0)	261	2	1,294.2	15.5 (1.9, 55.8)
By HPV Type								
HPV 6/11/16/18-related	870	8	4,619.9	17.3 (7.5, 34.1)	261	0	1,298.6	0.0 (0.0, 28.4)
HPV 6-related	847	2	4,524.4	4.4 (0.5, 16.0)	255	0	1,273.4	0.0 (0.0, 29.0)
HPV 11-related	847	0	4,530.1	0.0 (0.0, 8.1)	255	0	1,273.4	0.0 (0.0, 29.0)
HPV 16-related	860	5	4,576.8	10.9 (3.5, 25.5)	260	0	1,293.0	0.0 (0.0, 28.5)
HPV 18-related	867	1	4,627.2	2.2 (0.1, 12.0)	259	0	1,285.9	0.0 (0.0, 28.7)
HPV 31/33/45/52/58-related	872	1	4,651.4	2.1 (0.1, 12.0)	261	2	1,294.2	15.5 (1.9, 55.8)
HPV 31-related	855	0	4,567.1	0.0 (0.0, 8.1)	259	0	1,289.2	0.0 (0.0, 28.6)
HPV 33-related	866	1	4,625.7	2.2 (0.1, 12.0)	259	0	1,294.0	0.0 (0.0, 28.5)
HPV 45-related	871	0	4,652.5	0.0 (0.0, 7.9)	261	0	1,298.6	0.0 (0.0, 28.4)
HPV 52-related	870	0	4,645.5	0.0 (0.0, 7.9)	261	2	1,294.2	15.5 (1.9, 55.8)
HPV 58-related	863	0	4,613.5	0.0 (0.0, 8.0)	259	0	1,293.2	0.0 (0.0, 28.5)

[a] For each study participant, person-years follow-up was calculated starting from the beginning of the long-term follow-up study (i.e., Month 42 visit) or the date when the study participant reached 16 years of age, whichever came later.

[b] A case of persistent infection is a participant who is positive to at least 1 common gene for the same HPV type in the HPV 6/11/16/18/31/33/45/52/58 PCR assay in 2 or more cervicovaginal/external genital swab, biopsy, or definitive therapy samples obtained at 2 or more consecutive visits at least 6 months (+ 1 month) apart.

[c] A case of persistent infection is a participant who is positive to at least 1 common gene for the same HPV type in the HPV 6/11/16/18/31/33/45/52/58 PCR assay in 3 or more cervicovaginal/external genital swab, biopsy, or definitive therapy samples obtained at 3 or more consecutive visits at least 6 months (+ 1 month) apart.

N = Number of participants in the indicated group who received at least one vaccination of 9vHPV vaccine and consented/assented to long-term follow-up.

n = Number of participants with least one follow-up visit contributing to effectiveness evaluation.

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

CI = Confidence interval; HPV = Human papillomavirus.

Assessors comment: The results of persistent Gardasil 9 targeted HPV infections 8 vs 10 years follow-up:

	N 8 years FU	Cases 8 years FU	Cases/ N 8 years	N 10 years FU	Cases 10 years FU	Cases/ N 10 years

Persistent HPV > 6 months women	856	14	0.016	872	24	0.028
Persistent HPV > 12 months women	856	7	0.008	872	9	0.010
Persistent HPV > 6 months men	251	3	0.012	261	7	0.027
Persistent HPV > 12 months men	251	1	0.004	261	2	0.008

The number of persistent infections (>6 months) increased about two-fold at 10 years follow-up compared to the 8 years follow-up among both women and men. It is not possible to conclude from these data if this is due to waning protection or from increased exposure. The study cohort, which was at 9-15 years of age at vaccination start is now, after 10 years FU, between 20-26 years old, which is a sexually active age.

6.3. Discussion

9vHPV vaccine induced strong immune response with high levels of antibodies for all vaccine included HPV types. These antibodies persisted at least 10 years following vaccination with 9vHPV vaccine as measured with a binding assay. Over time, GMT levels and seropositivity rates declined through an expected natural course. After 10 years, the vaccine induced antibodies are still detectable among more than 80 % of participants, depending on HPV type. There has not been a remarkable drop of antibody level or seropositivity from month 90 to month 126 indicating that antibody level is rather stable between 8 to 10 years.

In case of 9vHPV study in younger cohort (9-15 at vaccination initiation) **V503-002-20** there was no possible break through case identified during 10 years of follow-up. On the other hand, this cohort has not reached the age when the cervical lesions are usually discovered (30+).

During this study, persistent HPV infections were noted in some cases. During the 8 years follow-up, when 856 women had been sampled at least once, eleven females had HPV 16, and 3 women had one of each HPV 6, 18 and 33 infections which persisted more than 6 months. Seven HPV 16 infections were cleared, but the rest of these HPV infections persisted 12 months. At 8 years follow-up, 251 men had been sampled and three males had 6 months of persistence of HPV type HPV 11, 45 and 52. In one case, HPV 52 infection persisted 12 months.

According to the final analysis at 10 years of follow-up, 16 additional women compared to 8 years follow-up were sampled (altogether 872) and additional persistent HPV infections appeared. HPV 16 was altogether persistent more than 6 months in 17 women and more than 12 months in 5 women. HPV 6 persisted more than 6 months in 4 women and 12 months in 2 women. Also one women had HPV 58 infection, which persisted more than 6 months.

Among 8 males, HPV11 (1), HPV 31 (2), HPV 45 (1) and HPV 52 (4) persisted more than 6 months, whereas in 2 males HPV 52 persisted more than 12 months.

The number of infections increase compared to the earlier observation-point. It is not possible to conclude

if this is due to waning protection, or due to increased exposure. As this cohort was very young at the vaccination time it is unlikely that these infections were there already before vaccination.

7. Clinical Safety aspects

This application is in support of an update to the PI for the 9vHPV vaccine and includes Protocol V503-002-20. Protocol V503-002-20 is a LTFU extension of Protocol V503-002, to assess the long-term immunogenicity, effectiveness, and safety of the 9vHPV vaccine through 10 years postdose 3 (Month 126). Eligible participants included girls and boys enrolled in the V503-002 base study aged 9 to 15 years who received a 3-dose regimen of 9vHPV vaccine at Day 1, Month 2, and Month 6. No vaccinations were administered during the study extension. The final analysis (at Month 126) is included in this application.

7.1. Methods – analysis of data submitted

Safety Population
All safety analyses were performed on the all-participants-as-treated population, which was defined as all enrolled participants who received at least 1 dose of the study vaccine and had a safety follow-up.

Serious Adverse Events
SAEs included those events that met standard definitions for SAEs (ie, resulted in death, was life threatening, resulted in persistent or significant disability/incapacity, resulted in or prolonged existing inpatient hospitalization, was a congenital anomaly/birth defect, or was another important medical event) as well as cancer and overdose.
Adverse events resulting in death and SAEs that were considered by the investigator to be vaccine- or procedure-related occurring at any time during the study were to be reported to the Sponsor.

Pregnancy Outcomes
Throughout the study, pregnancies were to be followed to outcome. Pregnancy outcomes were reported to the Sponsor. SAEs in infants born to study participants were collected throughout the study and followed to outcome.

Overall Extent of Exposure
Measures of extent of exposure did not apply to the V503-002-20 study because vaccinations were not administered in the LTFU study.
The 1272 participants enrolled in the V503-002-20 study (971 female and 301 male) all received 3 doses of 9vHPV vaccine in the V503-002 base study.

7.2. Results

Serious Adverse Events
No vaccine-related or procedure-related SAEs were reported during the LTFU.
One participant died during the LTFU. The cause of death was disseminated tuberculosis (SAE, onset over eight and a half years post dose 3). The death was considered not related to study vaccination or procedures.
Although not required by the protocol, 1 SAE of 'abortion threatened' at over four and a half years post dose 3, considered not related to the vaccine or study procedures, was reported in 1 participant during study V503-002-20.

Pregnancy Outcomes
The safety profile of the 9vHPV vaccine with respect to pregnancy outcomes has been previously established based on a combined analysis of 7 Phase 3 clinical studies including more than 1500

pregnancies.
Known outcomes were reported for 240 pregnancies in Protocol V503-002-20. Most pregnancies resulted in live births. Spontaneous abortions (fetal loss before 20 weeks of gestation) and late fetal deaths (fetal death after 20 weeks of gestation) were reported for 9.6% (23/240) and 0.4% (1/240) of the pregnancies with known outcomes, respectively. The proportion of pregnancies with live birth that resulted in a congenital anomaly was 3.3% (8/240). Overall, the proportions of pregnancies that resulted in adverse outcomes of spontaneous abortion, late fetal death, or congenital anomaly in the study were within ranges reported in the general population. These results do not change the safety profile previously established.
Eight pregnancies in Protocol V503-002-20 resulted in live births in which the infants were diagnosed with congenital anomalies. These congenital anomalies included 1 case of unspecified congenital heart disease, 4 cases of congenital ankyloglossia, 1 case of syndactyly, 1 case of cleft lip and palate, and 1 case of trisomy 21. All these congenital anomalies occurred in pregnancies with an estimated date of conception >2 years postvaccination. None of these congenital anomalies were considered related to the study vaccine.
A total of 35 SAEs were reported in infants of 17 vaccinated female participants enrolled in Protocol V503-002-20 from the Month 36 visit through the end of the study. None of these SAEs were considered related to the study vaccine.
Narratives for all the SAEs reported in infants were provided.

7.3. Discussion

No vaccine-related or procedure-related SAEs were reported during the LTFU as expected as such AEs appear in frame of the few months from vaccination and not years after. One participant died due to the tuberculosis almost 9 years after last dose of Gardasil 9 and is clearly unrelated to the vaccination. Same applies to the case of "abortion threatened" 4.5 years post dose 3. The pregnancy outcomes were as expected, and Gardasil 9 had no influence for these.

We conclude that administration of a 3-dose regimen of 9vHPV vaccine to girls and boys 9 to 15 years of age is generally well tolerated through 10 years postvaccination.

8. Changes to the Product Information

As a result of this variation, section 5.1 of the SmPC is updated to include information on long-term effectiveness and immunogenicity data following the final results of the Gardasil 9 study V503-002-20 listed as a category 3 study in the RMP. In addition, the applicant took the opportunity to make some minor editorial changes (spacings) and included the updated long term follow-up data already approved for the qHPV vaccine following V501-167 extension study.

The main SmPC changes in section 5.1 proposed by the MAH were the following:

Long-term effectiveness studies

In Protocol 002 extension study, no cases of high-grade intraepithelial neoplasia or genital warts were observed through ~~8.2~~11.0 years postdose 3 (median follow-up of ~~7~~10.~~6~~ 0 years) in girls (n = ~~864~~872) and through ~~8.1~~10.6 years postdose 3 (median follow-up of ~~7.6~~9.9 years) in boys (n = 26~~21~~) who were aged 9 to 15 years at time of vaccination with Gardasil 9.

Persistence of immune response to Gardasil 9

In long-term follow-up extension of clinical studies Protocols 001 and 002, persistence of antibody responses was observed:

- for at least 5 years in women who were aged 16 to 26 years at time of vaccination with Gardasil 9, depending on HPV type, 78 to100 % of subjects were seropositive; however, efficacy was maintained in all subjects regardless of seropositivity status for any vaccine HPV type through the end of the study (up to 67 months postdose 3, median follow-up duration of 43 months postdose 3),
- for at least ~~7~~ 10 years in girls and boys who were aged 9 to 15 years at time of vaccination with Gardasil 9; depending on HPV type, ~~91~~ 81 to ~~99~~ 98 % of subjects were seropositive.

Assessor´s comment: the updates are based on 10 years-follow-up of study V503-002-20. The updates are in agreement with the presented data and are therefore acceptable, but the Long-term effectiveness paragraph should also mention the data on persistent infection as no cases would be expected in the study cohort due to the limited sample size. Also, persistent infection was a key effectiveness endpoint of this study.

Immune responses to Gardasil 9 using a 2-dose schedule in individuals 9 through 14 years of age

In a clinical trial, persistence of antibody response has been demonstrated for at least ~~5~~ 10 years in girls aged 9 to13 years who received 2 doses of qHPV vaccine.

Assessor´s comment: the update bases on 10 years-follow-up of study V501-167. The updates are in agreement with the presented data during the previous procedure EMEA/H/C/000703/II/0087 for Gardasil and are therefore acceptable.

Based on the above assessment remarks, the resulting text for Section 5.1 is therefore endorsed:

Long-term effectiveness studies

A subset of subjects is being followed up for 10 to 14 years after Gardasil 9 vaccination for safety, immunogenicity, and effectiveness against clinical diseases related to the HPV types in the vaccine.

In the long-term extensions of clinical studies Protocols 001 and 002, effectiveness was observed in the PPE population. The PPE population consisted of individuals:

- who received all 3 vaccinations within 1 year of enrolment, without major deviations from the study protocol,
- who were seronegative to the relevant vaccine HPV type(s) prior to dose 1 and among women aged 16 to 26 years, PCR negative to the relevant vaccine HPV type(s) prior to dose 1 through one month postdose 3 (Month 7).

In Protocol 001 registry study, no cases of vaccine HPV types related high-grade CIN were observed through 9.5 years postdose 3 (median follow-up of 6.3 years) in women (n = 1,448) who were aged 16 to 26 years at time of vaccination with Gardasil 9.

In Protocol 002 extension study, no cases of high-grade intraepithelial neoplasia or genital warts were observed through ~~8.2~~11.0 years postdose 3 (median follow-up of ~~7~~10.~~6~~ 0 years) in girls (n = ~~864~~872) and through ~~8.1~~10.6 years postdose 3 (median follow-up of ~~7.6~~9.9 years) in boys (n = 262~~1~~) who were aged 9 to 15 years at time of vaccination with Gardasil 9. Incidence rates of vaccine HPV types related 6-month persistent infections in girls and boys observed during the study were 52.4 and 54.6 per 10,000 person-years, respectively, and within ranges of incidence rates expected in vaccinated cohorts of similar age (based on results from previous efficacy studies of Gardasil 9 and qHPV vaccine).

Please see Attachment 1 which includes all agreed changes to the Product Information.

9. Request for supplementary information

9.1. Major objections

Clinical aspects

None.

9.2. Other concerns

Clinical aspects

1. The MAH is asked to describe in SmPC the outcome of the key effectiveness endpoint of the study V503-002-20, incidence of the persistent HPV infections from the study start until in the end of the study (10 y FU).

10. Assessment of the responses to the request for supplementary information

10.1. Major objections

10.2. Other concerns

Clinical aspects

Question 1

1. The MAH is asked to describe in SmPC the outcome of the key effectiveness endpoint of the study V503-002-20, incidence of the persistent HPV infections from the study start until in the end of the study (10 y FU).

Summary of the MAH's response

The updated SmPC section 5.1, Long-term effectiveness studies**:**

In Protocol 002 extension study, no cases of high-grade intraepithelial neoplasia or genital warts were observed through ~~8.2~~11.0 years postdose 3 (median follow-up of ~~7~~10.6~~-~~0 years) in girls (n = ~~864~~872) and through ~~8.1~~10.6 years postdose 3 (median follow-up of ~~7.6~~9.9 years) in boys (n = 262~~1~~) who were aged 9 to 15 years at time of vaccination with Gardasil 9. Incidence rates of vaccine HPV types related 6-month persistent infections in girls and boys observed during the study were 52.4 and 54.6 per 10,000 person-years, respectively, and within ranges of incidence rates expected in vaccinated cohorts of similar age (based on results from previous efficacy studies of Gardasil 9 and qHPV vaccine).

Rapporteur's comment
The MAH is asked to describe in the SmPC the outcome of the key effectiveness endpoint of the study V503-002-20, incidence of the persistent HPV infections from the study start until in the end of the study (10 y FU).

MAH response
The MAH has included a description of the HPV-related infections. In support of this description, please see the Clinical Overview, section 4.2.2 of module 2.5 submitted with the initial sequence of this variation application.

Assessment of the MAH's response:

The MAH has updated the SmPC according to the request by adding incidence rates of persistent HPV infections.

Conclusion: Issue resolved

11. Attachments

1. Product Information (changes highlighted) as adopted by the CHMP on 24 March 2022.