This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned in this report, healthcare professionals should consult local prescribing information for the product approved in their country.

1 Synopsis

MSD K.K.	Clinical Study Report Synopsis	(For national authority use only)
V503 [Nine-valent HPV (Type 6, 11, 16, 18, 31, 33, 45,52 and 58) L1 Virus-Like Particle (VLP) Vaccine, Injection, Prevention of cervical, vulvar, and vaginal cancers and related precancers, external genital lesions, and persistent infection caused by Human Papillomavirus (HPV) 6, 11, 16, 18, 31, 33, 45, 52, and 58.]	Referring to Part of the Dossier Volume: Page:	

PROTOCOL TITLE: A Phase III Open-label, Safety, Tolerability and Immunogenicity Study of a 9-Valent Human Papillomavirus (HPV) L1 Virus-Like Particle (VLP) Vaccine Administered to 9- to 15-Year-Old Japanese preadolescent and adolescent girls

Protocol No.:008

INVESTIGATOR(S)/STUDY CENTER(S): [redacted] and others. Multicente (3 sites))

STUDY DURATION:

- 14-Jan-2011 (the date when the first subject started the study vaccination) to 10-Aug-2013 (the predefined last visit date of the last subject [Visit 7, Month 30])

CLINICAL PHASE: Ⅲ

DURATION OF TREATMENT: Vaccination at Day 1, Month 2, and Month 6. Total 3 vaccinations.

OBJECTIVES:

Primary

1) To evaluate the safety and tolerability of V503 when administered to 9- to 15-year-old girls.
2) To estimate the immune response for the vaccine HPV types (6, 11, 16, 18, 31, 33, 45, 52 and 58) at 4 weeks post dose 3 using seroconversion rates.

Secondary

1) To demonstrate that administration of V503 induces non-inferior GMTs for serum anti-HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58 in girls aged 9- to 15-year-old compared with those in Japanese women aged 16- to 26-year-old in Phase IIb/III study (Protocol 001) for V503 at 4 weeks post dose 3.
2) To describe the persistence of the serum antibody titers for the vaccine HPV types 24 months following the third dose of V503.
3) To estimate the immune response for the vaccine HPV types (6, 11, 16, 18, 31, 33, 45, 52 and 58) at 4 weeks post dose 3 using geometric mean titers (GMTs)

Study Design:

This is an open-label study to evaluate the safety, tolerability and immunogenicity of V503.

Subject Disposition:

Subject Disposition (Day 1 to Month 7)

	Total	
	n	(%)
Subjects in population	100	
Vaccinated at		
Vaccination 1	100	(100.0)
Vaccination 2	99	(99.0)
Vaccination 3	99	(99.0)
Study Disposition		
COMPLETED	99	(99.0)
DISCONTINUED	1	(1.0)
WITHDRAWAL BY SUBJECT	1	(1.0)
ADVERSE EVENT	0	(0.0)
LOST TO FOLLOW-UP	0	(0.0)
PROTOCOL VIOLATION	0	(0.0)
Each subject is counted once for Study Disposition.		

DOSAGE/FORMULATION NOS:

Subjects received a 0.5 mL intramuscular dose of V503 at Day 1, Month 2 and Month 6. Lot numbers and dosage for the clinical material can be found in a table below.

V503 Formulation

Vaccine	Potency	Lot No.	Package	Expiration date
V503	HPV 6/11/16/18/31/33/45/52/58 = 30/40/60/20/20/20/20/20 µg plus aluminum adjuvant 500 µg/0.5 mL	[redacted]	89473	2012/2/29

DIAGNOSIS/INCLUSION CRITERIA: To receive the first study vaccination, subjects should meet all inclusion criteria:

1) Subject is female, between the age of 9 years and 0 days and 15 years and 364 days on the day of the first study vaccination.
2) Subject is judged to be in good physical health on the basis of medical history, physical examination, and laboratory results.
3) Parent/legal guardian and subject fully understand study procedures, alternative treatments available, the risks involved with the study, and voluntarily agree to participate by giving written informed consent. In addition, written assent of the subject herself is to be obtained as far as possible.
4) Subject's parent/legal guardian is able to read, understand, and complete the vaccination report card.
5) Subject's parent/guardian agrees to provide study personnel with a primary telephone number

as well as an alternate telephone number for follow-up purposes

6) Subject must not yet have had coitarche and does not plan on becoming sexually active during the Day 1 through Month 7 period.

EVALUATION CRITERIA:

IMMUNOGENICITY MEASUREMENTS

Seroconversion rate for each of the vaccine HPV types (Types 6, 11, 16, 18, 31, 33, 45, 52 and 58)
Serum antibody titer to each of the vaccine HPV types (Types 6, 11, 16, 18, 31, 33, 45, 52 and 58) (Competitive Luminex Immunoassay [cLIA])

SAFETY MEASUREMENTS

Adverse experiences, vaccine-related adverse experiences and oral temperature

STATISTICAL PLANNING AND ANALYSIS:

IMMUNOGENICITY

The primary immunogenicity endpoints are seroconversion percentages by Month 7 to each of HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58. Seroconversion is defined as changing serostatus from seronegative to seropositive. A subject with a cLIA titer at or above the serostatus cutoff for a given HPV type is considered seropositive for that type. The secondary endpoint is to demonstrate that administration of V503 induces non-inferior GMTs for each HPV types in girls aged 9- to 15-year-old compared with those in Japanese women aged 16- to 26-year-old enrolled in V503-001 at 1 month Postdose 3. The statistical criterion requires that the lower bound of two-sided 95% confidence interval of GMT ratio be greater than 0.5 for each HPV type. GMTs and seroconversion percentages at Months 12, 24 and 30 will be summarized to assess the persistence of immune responses. As an additional analysis, the reverse cumulative distribution of anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 cLIA titers, respectively, at Month 7 was generated to examine the distribution. In addition, point estimate for Month 7 GMTs will be provided for 9-12 and 13-15 year old age strata, and GMTs in this study were compared with those of 9- to 15-year-old subjects enrolled in PN002. The main immunogenicity analysis is based on the Per Protocol Immunogenicity (PPI) population, which includes subjects without protocol violations. To be included in this population, subjects must: (1) Have received all 3 vaccinations with the correct dose of the correct clinical material, and each vaccination visit must occur within acceptable day ranges (2) Have provided Month 7 serology result within acceptable day ranges (3) Be seronegative to the appropriate HPV type at Day 1 (4) Have no other protocol violations that could interfere with the evaluation of subject's immune response to the study vaccine.

SAFETY

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

RESULTS:

IMMUNOGENICITY

1) Seroconversion rate for each HPV types

The serocoversion rate for each of 9 HPV types (Types 6, 11, 16, 18, 31, 33, 45, 52 and 58) at 1 month after postdose 3 (Month 7) is shown below. The seroconversion rate for each of 9 HPV types were 100%, and the point estimation of seroconversion rate for all 9 HPV types are over 90% which met predefined success criteria.

Summary of Seroconversion Rate for Each of the HPV Types at Month 7
(Per Protocol Immunogenicity Population†)

HPV-Type	Subjects (N=100)				
		Seropositivity			
	n	m	Percent‡	95% CI	p-Value‡
Anti-HPV 6	97	97	100%	(96.3%, 100%)	<0.001
Anti-HPV 11	97	97	100%	(96.3%, 100%)	<0.001
Anti-HPV 16	99	99	100%	(96.3%, 100%)	<0.001
Anti-HPV 18	98	98	100%	(96.3%, 100%)	<0.001
Anti-HPV 31	97	97	100%	(96.3%, 100%)	<0.001
Anti-HPV 33	98	98	100%	(96.3%, 100%)	<0.001
Anti-HPV 45	99	99	100%	(96.3%, 100%)	<0.001
Anti-HPV 52	99	99	100%	(96.3%, 100%)	<0.001
Anti-HPV 58	95	95	100%	(96.2%, 100%)	<0.001

† 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 for the relevant HPV-type(s), and had a Month 7 serum sample collected within an acceptable day range.
‡ Percent represents proportion of subjects 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.
‡ 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.
N = Number of subjects 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

2) Geometric Mean Titers (GMT) to Each of the HPG types

Analytical results of GMTs to each of the HPV types (Types 6, 11, 16, 18, 31, 33, 45, 52 and 58) at 1 months Postdose 3(Month 7) are shown below. Anti-HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58 were 1,836.5 mMU/mL, 1,331.3 mMU/mL, 6.823.6 mMU/mL, 2,159.9 mMU/mL, 2,052.5 mMU/mL, 994.8 mMU/mL, 811.0 mMU/mL, 1,069.1 mMU/mL and 1,488.2 mMU/mL, respectively.

Summary of Geometric Mean Titers to Each of the HPV types at Month 7
(Per Protocol Immunogenicity Population†)

	Subjects (N=100)		
Assay (cLIA)	n	GMT (mMU/mL)	95% CI
Anti-HPV 6	97	1,836.5	(1,597.7, 2,111.0)
Anti-HPV 11	97	1,331.3	(1,135.0, 1,561.4)
Anti-HPV 16	99	6,823.6	(5,907.9, 7,881.2)
Anti-HPV 18	98	2,159.9	(1,803.8, 2,586.3)
Anti-HPV 31	97	2,052.5	(1,735.9, 2,426.8)
Anti-HPV 33	98	994.8	(857.2, 1,154.4)
Anti-HPV 45	99	811.0	(679.7, 967.6)
Anti-HPV 52	99	1,069.1	(908.4, 1,258.4)
Anti-HPV 58	95	1,488.2	(1,285.0, 1,723.4)

†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 for the relevant HPV-type(s), and had a Month 7 serum sample collected within an acceptable day range.
N = Number of subjects 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.

3) Comparison with GMTs in 16- to 26-year old Japanese females (PN001)
The results of comparison with GMTs between each age strata (9-15 years old and 16-26 years old) are shown below. The ratio of GMTs at 1 month Postdose 3 (Month 7) in the 9- to 15-year-old females and 16- to 26-year-old females for HPV Type 6, 11, 16, 18, 31, 33, 45, 52 and 58 were 2.19 (1.78, 2.68), 2.18 (1.75, 2.72), 2.55 (2.09, 3.13), 3.14 (2.43, 4.05), 3.05 (2.43, 3.84), 2.50 (2.04, 3.05), 3.14 (2.45, 4.01), 3.49 (2.78, 4.38) and 3.24 (2.65, 3.96), respectively. The lower bound of 95% CI was greater than 0.5. Therefore, the GMTs induced by V503 administration to the 9- to 15-year-old females were at least equal to those observed in the 16- to 26-year-old Japanese females (PN001).

Comparison with GMTs between Each Age Strata
（Per Protocol Immunogenicity Population）

	Comparison Group					
	Subjects aged 9 to 15 (Comparison Group A) (N = 100)		Subjects aged 16 to 26 (Comparison Group B) (N = 127)		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	97	1,836.5	93	839.7	2.19 (1.78, 2.68)	<0.001
Anti-HPV 11	97	1,331.3	93	611.1	2.18 (1.75, 2.72)	<0.001
Anti-HPV 16	99	6,823.6	96	2,672.7	2.55 (2.09, 3.13)	<0.001
Anti-HPV 18	98	2,159.9	99	688.7	3.14 (2.43, 4.05)	<0.001
Anti-HPV 31	97	2,052.5	104	672.3	3.05 (2.43, 3.84)	<0.001
Anti-HPV 33	98	994.8	109	398.3	2.50 (2.04, 3.05)	<0.001
Anti-HPV 45	99	811.0	111	258.5	3.14 (2.45, 4.01)	<0.001
Anti-HPV 52	99	1,069.1	98	306.3	3.49 (2.78, 4.38)	<0.001
Anti-HPV 58	95	1,488.2	95	459.6	3.24 (2.65, 3.96)	<0.001

‡The estimated GMT, fold difference, associated confidence intervals, and p-value are based on an ANCOVA model with a response of the natural log of individual titers and fixed effects for comparison group.
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 dif
ference 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.

4) Comparison with GMTs between Japanese (PN008) and non-Japanese (PN002) aged 9 to 15 years

The GMTs for each of the HPV types at Month 7 in this study (PN008) and the ex-Japan study (PN002) were comparable, and no substantial differences were found as below.

Comparison with GMTs in 9- to 15-year old Japanese and non-Japanese for each of the HPV types
（Per Protocol Immunogenicity Population）

	Comparison Group				Estimated Fold Difference	
	Japanese (Comparison Group A) (N = 100)		Non-Japanese (Comparison Group B) (N = 640)			
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	97	1,836.5	1,597	1,715.4	1.07 (0.90, 1.28)	<0.001
Anti-HPV 11	97	1,331.3	1,597	1,295.1	1.04 (0.87, 1.25)	<0.001
Anti-HPV 16	99	6.823.6	1,627	6,979.8	0.96 (0.81, 1.15)	<0.001
Anti-HPV 18	98	2,159.9	1,641	2,153.7	1.04 (0.84, 1.28)	<0.001
Anti-HPV 31	97	2,052.5	1,617	1,891.6	1.09 (0.89, 1.33)	<0.001
Anti-HPV 33	98	994.8	1,637	980.4	1.05 (0.88, 1.26)	<0.001
Anti-HPV 45	99	811.0	1,647	714.4	1.10 (0.88, 1.38)	<0.001
Anti-HPV 52	99	1,069.1	1,642	932.9	1.10 (0.91, 1.33)	<0.001
Anti-HPV 58	99	1,488.2	1,630	1,286.7	1.16 (0.97, 1.41)	<0.001

[†] The per-protocol immunogenicity population includes all subjects who meet the PPI criteria in relevant studies.
[‡] 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 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.

5) Persistence of immune responses

The GMTs to the vaccine HPV types (Type 6, 11, 16, 18, 31, 33, 45, 52 and 58) reached a peak at Month 7 and then decreased until Month 30. However, it was confirmed that the GMTs to each HPV types were persistent at Month 30 (1010.3 to 1001.9 mMU/mL).

SAFETY

A summary of clinical adverse experiences occurred in the study is given below.

The incidence of clinical adverse experiences Days 1 to 15 following any vaccination was 97.0% (97/100 subjects). The incidence of injection-site adverse experiences was high. The incidence of vaccine-related clinical adverse experiences was 96.0% (96/100 subjects). The injection-site adverse experiences were occurred in 95 subjects. The most common injection-site adverse experience was injection-site pain (93%: 93/100 subjects), the second most common adverse experience was injection-site swelling (42%: 42/100 subjects) and the third most common adverse experience was injection-site erythema (33%: 33/100 subjects). The severe injection-site adverse experiences are injection-site pain (3.0%: 3/100 subjects) and swelling (10%: 10/100 subjects). 12 out of 13 subjects recovered within 8 days after onset. The incidence rate of vaccine related systemic adverse experiences was 14.0% (14/100 subjects), and the incidence rates of systemic adverse experiences occuerd in 2 or more subjects were pyrexia (3.0%: 3/100 subjects), abdominal pain, nausea, headache and hypoaesthesia (2.0%, 2/100 subjecsts, respectively) in order of descending prevalence. The intensity of all systemic adverse experiences was mild in intensity with exceptions of moderate tinnitus, pain in extremity, Herpes zoster and pyrexia. Tinnitus and pain in extremity of moderate intensity were observed 2 days after the first vaccination and resolved after 2 days. Pyrexia and Herpes zoster were observed 9 days and 10 days after the first vaccination, and resolved after 5 days and 17 days, respectively.

There was no serious adverse experience, death, discontinuation due to an adverse experience and pregnancy. Administration of 3-dose regimen of V503 to 9- to 15-year-old is generally well tolerated.

Clinical Adverse Experience Summary
(Day 1 to 15 Following Any Vaccination Visit)

	Subjects	
	n	(%)
Subjects in population with follow-up	100	
with one or more adverse events	97	(97.0)
injection-site	95	(95.0)
non-injection-site	35	(35.0)
with no adverse event	3	(3.0)
with vaccine-related† adverse events	96	(96.0)
injection-site	95	(95.0)
non-injection-site	14	(14.0)
with serious adverse events	0	(0.0)
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.

CONCLUSION:

1) Administration of a 3-dose regimen of V503 to female subjects 9 to 15 years of age showed high GMTs and 100% of seroconversion rates for vaccine HPV types (Types 6, 11, 16, 18, 31, 33, 45, 52 and 58) at 1 month after Postdose 3. Administration of a 3-dose regimen of V503 induced robust immune responses against each of the HPV types.
2) The serum antibody response to each HPV types (Types 6, 11, 16, 18, 31, 33, 45, 52 and 58) at 1 month after Postdose 3 in 9- to 15-year-old Japanese female subjects was at least equal to that observed in 16- to 26-year-old Japanese female subjects (PN001).
3) The GMTs induced after administration of a 3-dose regimen of V503 was similar between Japanese and non-Japanese (PN002) subjects 9 to 15 years of age.
4) The serum antibody response to each of the HPV types (Types 6, 11, 16, 18, 31, 33, 45, 52 and 58) was persistent at 2 years after 3-dose regimen of V503 (Month 30).
5) Administration of 3-dose regimen of V503 to female 9 to 15 years of age is generally well tolerated.