3º CUERPO

346-13-4

Appendix 2.5: 16

Analysis of Efficacy Against HPV 6/11/16/18-Related EGL by Sexual Orientation, HPV Type, and Lesion Type (Per-Protocol Efficacy Population) (Protocol 020)

Endpoint	qHPV Vaccine (N=2,025) n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Placebo (N=2,030) n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Observed Efficacy (%)	95% CI
HPV 6/11/16/18-Related EGL	1,394	3	3,109.2	0.1	1,404	32	3,106.0	1.0	90.6	(70.1, 98.2)
By Sexual Orientation										
HM Subjects	1,200	2	2,722.4	0.1	1,196	26	2,689.7	1.0	92.4	(69.6, 99.1)
MSM Subjects	194	1	386.9	0.3	208	6	416.3	1.4	82.1	(-47.8, 99.6)
By HPV Type										
HPV 6-Related EGL	1,242	3	2,779.8	0.1	1,243	19	2,790.3	0.7	84.2	(46.2, 97.0)
HPV 11-Related EGL	1,242	1	2,781.2	0.0	1,243	11	2,790.7	0.4	90.9	(37.2, 99.8)
HPV 16-Related EGL	1,292	0	2,883.5	0.0	1,270	3	2,841.1	0.1	100	(-138.4, 100)
HPV 18-Related EGL	1,331	0	2,978.0	0.0	1,352	1	3,013.4	0.0	100	(-3846.4, 100)

Merck Sharp & Dohme (Argentina) Inc.
Apoderado

MERCK SHARP & DOHME ARG. INC.
Farm. Sebastián Darío Goldentul
DIRECTOR TECNICO
MATRICULA NACIONAL 15436

601

Analysis of Efficacy Against HPV 6/11/16/18-Related EGL by Sexual Orientation, HPV Type, and Lesion Type (Per-Protocol Efficacy Population) (Protocol 020) (Cont.)

Endpoint	qHPV Vaccine (N=2,025)				Placebo (N=2,030)				Observed Efficacy (%)	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		
By Lesion Type										
Condyloma	1,394	3	3,109.2	0.1	1,404	28	3,108.0	0.9	89.3	(65.3, 97.9)
PIN 1 or worse	1,394	0	3,112.2	0.0	1,404	4	3,124.9	0.1	100	(-52.1, 100)
PIN 1	1,394	0	3,112.2	0.0	1,404	2	3,126.6	0.1	100	(-434.9, 100)
PIN 2/3 or Cancer	1,394	0	3,112.2	0.0	1,404	2	3,125.1	0.1	100	(-434.7, 100)
PIN 2/3	1,394	0	3,112.2	0.0	1,404	2	3,125.1	0.1	100	(-434.7, 100)
Penile/Perianal/Perineal Cancer	1,394	0	3,112.2	0.0	1,404	0	3,126.8	0.0	NA	NA

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.

CI = Confidence interval; EGL = External genital lesions with a diagnosis of Condyloma, PIN, or Penile/Perianal/Perineal Cancer; HM = Heterosexual men; HPV = Human papillomavirus; MSM = Men having sex with men; PIN = Penile/Perianal/Perineal intraepithelial neoplasia; qHPV Vaccine = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine.

[Ref. 5.3.5.1: P020]

Appendix 2.5: 17

Analysis of Efficacy Against HPV 6/11/16/18-Related EGL by Sexual Orientation, HPV Type, and Lesion Type (Naïve to the Relevant HPV Type Population) (Protocol 020)

	qHPV Vaccine (N=2,025)				Placebo (N=2,030)					
Endpoint	n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Observed Efficacy (%)	95% CI
HPV 6/11/16/18-Related EGL	1,775	13	4,607.3	0.3	1,770	54	4,530.1	1.2	76.3	(56.0, 88.1)
By Sexual Orientation										
HM Subjects	1,501	11	3,961.4	0.3	1,497	42	3,880.0	1.1	74.3	(49.3, 88.1)
MSM Subjects	274	2	645.9	0.3	273	12	650.1	1.8	83.2	(24.7, 98.2)
By HPV Type										
HPV 6-Related EGL	1,603	10	4,186.4	0.2	1,607	36	4,152.2	0.9	72.4	(43.3, 87.8)
HPV 11-Related EGL	1,603	1	4,202.1	0.0	1,607	17	4,168.0	0.4	94.2	(62.8, 99.9)
HPV 16-Related EGL	1,674	1	4,372.0	0.0	1,649	4	4,269.2	0.1	75.6	(-146.7, 99.5)
HPV 18-Related EGL	1,713	2	4,471.2	0.0	1,715	1	4,449.3	0.0	-99.0	(-11641.5, 89.6)

Analysis of Efficacy Against HPV 6/11/16/18-Related EGL by Sexual Orientation, HPV Type, and Lesion Type (Naïve to the Relevant HPV Type Population) (Protocol 020) (Cont.)

Endpoint	qHPV Vaccine (N=2,025) n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Placebo (N=2,030) n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Observed Efficacy (%)	95% CI
By Lesion Type										
Condyloma	1,775	10	4,615.4	0.2	1,770	49	4,533.5	1.1	80.0	(59.9, 90.9)
PIN 1 or worse	1,775	4	4,619.2	0.1	1,770	5	4,578.0	0.1	20.7	(-268.4, 84.3)
PIN 1	1,775	2	4,624.8	0.0	1,770	3	4,579.7	0.1	34.0	(-476.3, 94.5)
PIN 2/3 or Cancer	1,775	2	4,623.1	0.0	1,770	2	4,579.7	0.0	0.9	(-1266.6, 92.8)
PIN 2/3	1,775	2	4,623.1	0.0	1,770	2	4,579.7	0.0	0.9	(-1266.6, 92.8)
Penile/Perianal/Perineal Cancer	1,775	0	4,628.8	0.0	1,770	0	4,581.4	0.0	NA	NA

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.

CI = Confidence interval; EGL = External genital lesions with a diagnosis of Condyloma, PIN, or Penile/Perianal/Perineal Cancer; HM = Heterosexual men; HPV = Human papillomavirus; MSM = Men having sex with men; PIN = Penile/Perianal/Perineal intraepithelial neoplasia; qHPV Vaccine = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine.

[Ref. 5.3.5.1: P020]

Appendix 2.5: 18

Analysis of Efficacy Against HPV 6/11/16/18-Related EGL by Sexual Orientation, HPV Type, and Lesion Type (Full Analysis Set) (Protocol 020)

Endpoint	qHPV Vaccine (N=2,025)				Placebo (N=2,030)				Observed Efficacy (%)	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 EGL	1,943	27	4,987.0	0.5	1,937	80	4,914.2	1.6	66.7	(48.0, 79.3)
By Sexual Orientation										
HM Subjects	1,653	21	4,314.4	0.5	1,648	57	4,244.9	1.3	63.8	(39.3, 79.1)
MSM Subjects	290	6	672.6	0.9	289	23	669.4	3.4	74.0	(34.4, 91.4)
By HPV Type										
HPV 6-Related EGL	1,943	21	4,998.3	0.4	1,937	52	4,943.2	1.1	60.1	(32.5, 77.1)
HPV 11-Related EGL	1,943	6	5,029.2	0.1	1,937	26	4,978.9	0.5	77.2	(43.2, 92.3)
HPV 16-Related EGL	1,943	3	5,029.6	0.1	1,937	11	4,998.9	0.2	72.9	(-2.6, 95.1)
HPV 18-Related EGL	1,943	2	5,035.7	0.0	1,937	3	5,008.5	0.1	33.7	(-478.8, 94.5)

Merck Sharp & Dohme (Argentina) Inc.

MERCK SHARP & DOHME ARG. INC.
Farm. Sebastian Dario Goldentul
DIRECTOR TECNICO
MATRICULA NACIONAL 15436

Merck Sharp & Dohme (Argentina) Inc.
Apoderado

Analysis of Efficacy Against HPV 6/11/16/18-Related EGL by Sexual Orientation, HPV Type, and Lesion Type (Full Analysis Set) (Protocol 020) (Cont.)

Endpoint	qHPV Vaccine (N=2,025) n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Placebo (N=2,030) n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Observed Efficacy (%)	95% CI
By Lesion Type										
Condyloma	1,943	24	4,997.5	0.5	1,937	74	4,918.9	1.5	68.1	(48.8, 80.7)
PIN 1 or worse	1,943	6	5,023.2	0.1	1,937	6	5,006.4	0.1	0.3	(-272.8, 73.4)
PIN 1	1,943	3	5,031.4	0.1	1,937	4	5,008.1	0.1	25.3	(-341.3, 89.1)
PIN 2/3 or Cancer	1,943	3	5,029.6	0.1	1,937	3	5,008.1	0.1	0.4	(-643.4, 86.7)
PIN 2/3	1,943	3	5,029.6	0.1	1,937	3	5,008.1	0.1	0.4	(-643.4, 86.7)
Penile/Perianal/Perineal Cancer	1,943	0	5,037.8	0.0	1,937	0	5,011.1	0.0	NA	NA

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.

CI = Confidence interval; EGL = External genital lesions with a diagnosis of Condyloma, PIN, or Penile/Perianal/Perineal Cancer; HM = Heterosexual men; HPV = Human papillomavirus; MSM = Men having sex with men; PIN = Penile/Perianal/Perineal intraepithelial neoplasia; qHPV Vaccine = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine.

[Ref. 5.3.5.1: P020]

MERCK SHARP & DOHME ARG. INC.
Farm. Sebastián Darío Goldentul
DIRECTOR TECNICO
MATRICULA NACIONAL 16436

606

Appendix 2.5: 19

Summary of Anti-HPV Geometric Mean Titers by Vaccination Group (Per-Protocol Immunogenicity Population) (Protocol 020)

Assay (cLIA v2.0) Study time	qHPV Vaccine (N=2,025) n	GMT (mMU/mL)	95% CI	Placebo (N=2,030) n	GMT (mMU/mL)	95% CI
Anti-HPV 6						
Day 1	1,092	< 7	(<7, <7)	1,108	< 7	(<7, <7)
Month 7	1,092	447.6	(422.6, 474.1)	1,108	< 7	(<7, <7)
Month 24	941	79.8	(75.8, 84.1)	949	< 7	(<7, <7)
Month 36	847	71.5	(67.5, 75.8)	834	< 7	(<7, <7)
Anti-HPV 11						
Day 1	1,092	< 8	(<8, <8)	1,107	< 8	(<8, <8)
Month 7	1,092	624.0	(594.1, 655.4)	1,107	< 8	(<8, <8)
Month 24	941	94.6	(90.0, 99.5)	948	< 8	(<8, <8)
Month 36	847	82.6	(78.3, 87.1)	833	< 8	(<8, <8)
Anti-HPV 16						
Day 1	1,135	< 11	(<11, <11)	1,127	< 11	(<11, <11)
Month 7	1,135	2,404.3	(2,272.2, 2,544.0)	1,127	< 11	(<11, <11)
Month 24	979	342.7	(324.7, 361.7)	951	< 11	(<11, <11)
Month 36	877	293.3	(276.5, 311.2)	839	< 11	(<11, <11)
Anti-HPV 18						
Day 1	1,174	< 10	(<10, <10)	1,202	< 10	(<10, <10)
Month 7	1,174	402.3	(380.2, 425.7)	1,202	< 10	(<10, <10)
Month 24	1,011	38.4	(36.0, 41.0)	1,010	< 10	(<10, <10)
Month 36	905	33.1	(30.9, 35.4)	882	< 10	(<10, <10)

The estimated GMTs and associated CIs are calculated using an ANOVA model with a term for vaccination group.
N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects contributing to the analysis.
ANOVA = Analysis of variance; CI = Confidence interval; cLIA = Competitive Luminex immunoassay; GMT = Geometric mean titer; HPV = Human papillomavirus; mMU = Milli Merck units; qHPV Vaccine = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine.

[Ref. 5.3.5.1: P020]

Merck Sharp & Dohme (Argentina) Inc.

MERCK SHARP & DOHME ARG. INC.
Farm. Sebastián Darío Goloantu
DIRECTOR TECNICO
MATRICULA NACIONAL 15436

609

Appendix 2.5: 20

Summary of Anti-HPV Percent Seroconversion by Vaccination Group
(Per-Protocol Immunogenicity Population) (Protocol 020)

Anti-HPV Response / Study Time	qHPV Vaccine (N=2,025)				Placebo (N=2,030)			
		Seroconversion				Seroconversion		
	n	m	Percent	95% CI	n	m	Percent	95% CI
HPV 6 cLIA ≥ 20 mMU/mL								
Day 1	1,092	0	0.0	(0.0%, 0.3%)	1,108	0	0.0	(0.0%, 0.3%)
Month 7	1,092	1,080	98.9	(98.1%, 99.4%)	1,108	18	1.6	(1.0%, 2.6%)
Month 24	941	855	90.9	(88.8%, 92.6%)	949	20	2.1	(1.3%, 3.2%)
Month 36	847	753	88.9	(86.6%, 90.9%)	834	26	3.1	(2.0%, 4.5%)
HPV 11 cLIA ≥ 16 mMU/mL								
Day 1	1,092	0	0.0	(0.0%, 0.3%)	1,107	0	0.0	(0.0%, 0.3%)
Month 7	1,092	1,083	99.2	(98.4%, 99.6%)	1,107	23	2.1	(1.3%, 3.1%)
Month 24	941	900	95.6	(94.1%, 96.9%)	948	13	1.4	(0.7%, 2.3%)
Month 36	847	796	94.0	(92.2%, 95.5%)	833	19	2.3	(1.4%, 3.5%)
HPV 16 cLIA ≥ 20 mMU/mL								
Day 1	1,135	0	0.0	(0.0%, 0.3%)	1,127	0	0.0	(0.0%, 0.3%)
Month 7	1,135	1,121	98.8	(97.9%, 99.3%)	1,127	20	1.8	(1.1%, 2.7%)
Month 24	979	970	99.1	(98.3%, 99.6%)	951	7	0.7	(0.3%, 1.5%)
Month 36	877	859	97.9	(96.8%, 98.8%)	839	18	2.1	(1.3%, 3.4%)

608

Summary of Anti-HPV Percent Seroconversion by Vaccination Group
(Per-Protocol Immunogenicity Population) (Protocol 020) (Cont.)

Anti-HPV Response / Study Time	qHPV Vaccine (N=2,025)				Placebo (N=2,030)			
		Seroconversion				Seroconversion		
	n	m	Percent	95% CI	n	m	Percent	95% CI
HPV 18 cLIA ≥ 24 mMU/mL								
Day 1	1,174	0	0.0	(0.0%, 0.3%)	1,202	0	0.0	(0.0%, 0.3%)
Month 7	1,174	1,143	97.4	(96.3%, 98.2%)	1,202	21	1.7	(1.1%, 2.7%)
Month 24	1,011	630	62.3	(59.2%, 65.3%)	1,010	12	1.2	(0.6%, 2.1%)
Month 36	905	516	57.0	(53.7%, 60.3%)	882	9	1.0	(0.5%, 1.9%)

Percent is calculated as 100*(m/n).

The CIs are computed based on exact methods.

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

n = Number of subjects contributing to the analysis.

m = Number of subjects with the indicated response.

CI = Confidence interval; cLIA = Competitive Luminex immunoassay; HPV = Human papillomavirus; mMU = Milli Merck units; qHPV Vaccine = Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine.

[Ref. 5.3.5.1: P020]

609

Appendix 2.5: 21

Clinical Adverse Experience Summary (Day 1 Through Entire Study Period Following Any Vaccination Visit)
Male Subjects 9 to 26 Years of Age in the Detailed Safety Population (Protocols 016, 018 and 020)

	qHPV (N=3093)		Placebo (N=2303)	
	n	(%)	n	(%)
Subjects in analysis population	3093		2303	
Subjects without follow-up	89		84	
Subjects with follow-up	3004		2219	
Number (%) of subjects:				
with no adverse experience	786	(26.2)	794	(35.8)
with one or more adverse experiences	2218	(73.8)	1425	(64.2)
injection-site adverse experiences	1927	(64.1)	1177	(53.0)
systemic adverse experiences	1121	(37.3)	732	(33.0)
with vaccine-related[1] adverse experiences	2049	(68.2)	1284	(57.9)
injection-site adverse experiences	1927	(64.1)	1176	(53.0)
systemic adverse experiences	528	(17.6)	337	(15.2)
with serious adverse experiences	13	(0.4)	11	(0.5)
with serious vaccine-related adverse experiences	0	(0.0)	0	(0.0)
who died	4	(0.1)	10	(0.5)

Merck Sharp & Dohme (Argentina) Inc.
Apoderado

MERCK SHARP & DOHME ARG. INC.
Farm. Sebastián Darío Goldentul
DIRECTOR TECNICO
MATRICULA NACIONAL 15436

Merck Sharp & Dohme (Argentina) Inc.

Clinical Adverse Experience Summary (Day 1 Through Entire Study Period Following Any Vaccination Visit)
Male Subjects 9 to 26 Years of Age in the Detailed Safety Population (Protocols 016, 018 and 020) (Cont.)

	qHPV (N=3093)		Placebo (N=2303)	
	n	(%)	n	(%)
discontinued[‡] due to an adverse experience	10	(0.3)	14	(0.6)
discontinued due to a vaccine-related adverse experience	4	(0.1)	3	(0.1)
discontinued due to a serious adverse experience	5	(0.2)	10	(0.5)
discontinued due to a serious vaccine-related adverse experience	0	(0.0)	0	(0.0)

[†] Determined by the investigator to be possibly, probably, or definitely related to the vaccine.
[‡] Discontinued = Subject discontinued from therapy.
Percentages are calculated based on the number of subjects with follow-up.

[Ref. 5.3.5.1: 1464, 2050, 2083, P016V1, P016V2, P018V1, P020]

MERCK SHARP & DOHME ARG. INC
Farm. Sebastián Darío Goldentul
DIRECTOR TÉCNICO
MATRICULA NACIONAL 15436

611

2.5 Clinical Overview

Merck Sharp & Dohme (Argentina) Inc.
Jose Avione
Apoderado

MERCK SHARP & DOHME ARG. INC.
Farm. Sebastian Mario Goldentul
DIRECTOR TECNICO
MATRICULA NACIONAL 15436

TABLE OF CONTENTS

	PAGE
LIST OF APPENDICES	3
2.5.1 Product Development Rationale	5
2.5.1.1 Pharmacologic Class	5
2.5.1.2 Chemical and Pharmaceutical Properties	5
2.5.1.3 Proposed Indications	5
2.5.1.4 Scientific Background	6
2.5.1.4.1 Public Health Burden of HPV-Related Clinical Disease	6
2.5.1.4.2 HPV Virology and Pathophysiology of HPV Infection	7
2.5.1.4.3 Epidemiology of HPV Infection – Impact on Clinical Trial Design	8
2.5.1.4.4 Study Endpoints in Efficacy Studies of qHPV in Women	8
2.5.1.4.4.1 Study Endpoints – Mid-Adult Women (24- to 45-Year-Old Women)	8
2.5.1.4.4.2 Other Important Endpoints	10
2.5.1.4.4.2.1 Overall Impact of Vaccination – Disease Cause by Vaccine or Non-Vaccine HPV Types	10
2.5.1.5 Overview: Clinical Development Program for qHPV Vaccine	10
2.5.1.6 Standard Research Procedures	11
2.5.1.7 Regulatory Guidance and Advice	12
2.5.1.8 Good Clinical Practices	12
2.5.2 Overview of Biopharmaceutics	12
2.5.3 Overview of Clinical Pharmacology	12
2.5.4 Overview of Efficacy and Immunogenicity	12
2.5.4.1 Clinical Efficacy	12
2.5.4.1.1 Program in Mid-Adult Women (MAW)	13
2.5.4.1.1.1 Overview – Protocol 019	13
2.5.4.1.1.2 Subject Disposition and Subject Accounting	13
2.5.4.1.1.3 Enrollment Characteristics	13
2.5.4.1.1.4 Efficacy Results – Protocol 019 (MAW)	13
2.5.4.1.1.5 Efficacy Conclusions – Protocol 019	21
2.5.4.2 Immunogenicity	22
2.5.4.2.1 Protocol 019: Phase III Study of qHPV vaccine in 24- to 45-Year Old Women (Mid-Adult Women, or MAW)	22
2.5.4.2.2 Persistence of Anti-HPV Responses	24
2.5.4.2.3 Conclusions Regarding the Immunogenicity of qHPV vaccine	24
2.5.5 Overview of Safety	24
2.5.5.1 Analysis of Adverse Experiences in Safety Population (24- to 45-Year-Old Subjects)	24
2.5.5.2 New Medical History in the Safety Population	25
2.5.5.3 Safety in Special Groups and Situations	26
2.5.5.3.1 Intrinsic Factors	26

Merck Sharp & Dohme (Argentina) Inc.
Jose [illegible]
Apoderado

MERCK SHARP & DOHME ARG. INC.
Farm. Sebastián Darío Goldentu
DIRECTOR TECNICO
MATRICULA NACIONAL 15436

TABLE OF CONTENTS (CONT.)

	PAGE
2.5.5.3.2 Extrinsic Factors	26
2.5.5.3.3 Outcome of Pregnancies	26
2.5.5.3.4 Administration of qHPV vaccine to Lactating Women	27
2.5.5.4 Postmarketing Safety Data	27
2.5.5.5 Overdose	28
2.5.5.6 Drug Abuse/Withdrawal and Rebound/Impairment of Mental Ability	28
2.5.5.7 Conclusions Regarding the Safety of qHPV vaccine	28
2.5.6 Benefits and Risks Conclusions	29
2.5.6.1 Overview	29
2.5.6.2 New Information Presented in the Current Application	30
2.5.6.3 Limitations and Risks	31
2.5.7 Literature References	34
2.5.8 Appendix	38

Merck Sharp & Dohme (Argentina) Inc.
José Perrone
Apoderado

MERCK SHARP & DOHME ARG. INC.
Farm. Sebastián Clario Goldentul
DIRECTOR TECNICO
MATRICULA NACIONAL 15436

LIST OF APPENDICES

		PAGE
Appendix 2.5: 1	Assessment of the Value of HPV 16/18-Related Persistent Infection as a Predictor of HPV 16/18-Related CIN 2/3, AIS, or Cervical Cancer (Protocol 012: MITT-2/Naive to the Relevant HPV Type Population)	38
Appendix 2.5: 2	Assessment of the Value of HPV 6/11/16/18-Related Persistent Infection as a Predictor of HPV 6/11/16/18-Related Disease (Naive to the Relevant HPV Type Population)	39
Appendix 2.5: 3	Listing of Protocols That Provided Updated or New Data for Cervical Disease Efficacy (Protocols 019)	40
Appendix 2.5: 4	Definition of Efficacy Populations in Protocol 019	43
Appendix 2.5: 5	Summary of Positivity by Serology or PCR to Multiple Vaccine HPV Types at Day 1 by Vaccination Group (Protocol 019)	44
Appendix 2.5: 6	Analysis of Efficacy Against HPV 6/11/16/18-Related Persistent Infection, CIN, and EGL (PPE, HNRT, and FAS Populations -- North America)	46
Appendix 2.5: 7	Characteristics with Respect to High-Risk HPV Type(s) Co-infections of Subjects Who Did Not Clear the HPV 16 Infection at Day 1 (Subjects Day 1 PCR Positive and Seronegative for HPV 16)	54
Appendix 2.5: 8	Analysis of Time-to-Clearance of HPV 16 Infection Among Subjects Who Were HPV 16 PCR Positive and Seronegative at Day 1 By High-Risk HPV Type Coinfection Status at Day 1 and Post-Day 1	55
Appendix 2.5: 9	Analysis of Efficacy Against HPV 6/11/16/18-Related Persistent Infection, CIN, and EGL (PPE, HNRT, and FAS Populations)	56
Appendix 2.5: 10	Assessment of the Value of HPV 6/11/16/18-Related Persistent Infection as a Predictor of HPV 6/11/16/18-Related Disease (Naive to the Relevant HPV Type Population, 6-month definition of Persistent Infection)	58

Merck Sharp & Dohme (Argentina) Inc.
Jessica Anne
Apoderada

MERCK SHARP & DOHME ARG. INC
Farm. Sebastián Darío Goldentul
DIRECTOR TECNICO
MATRICULA NACIONAL 15436

LIST OF APPENDICES (CONT.)

		PAGE
Appendix 2.5: 11	Analysis of Efficacy Against HPV 6/11/16/18-Related CIN or EGL Among Subjects Who Were PCR Negative/Seropositive for the Relevant Vaccine HPV Type(s) at Day 1 (Protocols 007, 013 and 015 Combined)	59
Appendix 2.5: 12	Analysis of Efficacy Against HPV 16/18-Related Persistent Infection Among Subjects Who Were PCR Negative/Seropositive for the Relevant Vaccine HPV Type(s) at Day 1 (Protocols 012 and 019 Combined)	60
Appendix 2.5: 13	Analysis of Efficacy Against HPV 6/11/16/18-Related CIN or EGL Among Subjects Who Were PCR Negative/Seropositive for the Relevant Vaccine HPV Type(s) at Day 1 (Protocols 007, 013 and 015 Combined)	61
Appendix 2.5: 14	Persistence of Anti-HPV 6 Immune Response† (Per-Protocol Immunogenicity Population – qHPV Vaccine Group)	62
Appendix 2.5: 15	Persistence of Anti-HPV 11 Immune Response† (Per-Protocol Immunogenicity Population – qHPV Vaccine Group)	63
Appendix 2.5: 16	Persistence of Anti-HPV 16 Immune Response† (Per-Protocol Immunogenicity Population – qHPV Vaccine Group)	64
Appendix 2.5: 17	Persistence of Anti-HPV 18 Immune Response† (Per-Protocol Immunogenicity Population – qHPV Vaccine Group)	65
Appendix 2.5: 18	Summary of Anti-HPV Percent Seroconversion by Vaccination Group (Per-Protocol Immunogenicity Population)	66

Merck Sharp & Dohme (Argentina) Inc.
Jose Perone
Apoderado

MERCK SHARP & DOHME ARG. INC
Farm. Sebastián Darío Goldentul
DIRECTOR TECNICO
MATRICULA NACIONAL 15436

2.5.1 Product Development Rationale

2.5.1.1 Pharmacologic Class

Quadrivalent Human Papillomavirus (HPV) (Types 6,11,16,18) recombinant vaccine, also referred to as qHPV vaccine, is a recombinant protein particulate (virus-like particle [VLP]) vaccine manufactured by Merck & Co., Inc. (West Point, Pennsylvania, U.S.A.) for the prevention of cancer, dysplasia, genital warts, and infection caused by HPV types targeted by the vaccine and related non-vaccine HPV types. All protocols presented by number are protocols that studied qHPV vaccine.

2.5.1.2 Chemical and Pharmaceutical Properties

The qHPV vaccine is prepared from the highly purified VLPs of the recombinant major capsid (L1) protein of HPV Types 6, 11, 16, and 18. The VLPs are adsorbed on amorphous aluminum hydroxyphosphate sulfate adjuvant. The formulation also includes sodium chloride, L-histidine, polysorbate 80, sodium borate, and water for injection. Each 0.5-mL dose is formulated to contain 20 µg HPV 6 L1 protein, 40 µg HPV 11 L1 protein, 40 µg HPV 16 L1 protein, and 20 µg HPV 18 L1 protein. The quadrivalent final container product is a sterile suspension for injection in a single-dose vial or a prefilled syringe. For each image, the fill volume permits administration of 0.5 mL of vaccine for intramuscular injection. The qHPV vaccine is not a live virus vaccine. It contains no viral deoxyribonucleic acid (DNA). It is incapable of causing infection.

2.5.1.3 Proposed Indications

The data presented in this supplemental Application confirm and extend the results submitted in prior Applications as follows:

Based on a robust demonstration of the efficacy of the qHPV vaccine when administered to 24- to 45-year-old women, it can be inferred that the efficacy conclusions resulting from the Phase III in young adult women can be applied to women through the age of 45 years at vaccination onset.

Accordingly, the current Application proposes the following indication for the qHPV vaccine:

The qHPV vaccine is a vaccine indicated in girls and women **9 to 45 years of age** for the prevention of cervical, vulvar and vaginal cancer, cervical dysplastic lesions, and genital warts caused by HPV. qHPV vaccine is indicated to prevent the following diseases:

Diseases caused by Human Papillomavirus (HPV) types 6, 11, 16, and 18:

- Cervical cancer, Vulvar cancer, and Vaginal cancer
- Genital warts (condyloma acuminata)

and the following precancerous or dysplastic lesions:

- Cervical adenocarcinoma *in situ* (AIS)
- Cervical intraepithelial neoplasia (CIN) grade 2 and grade 3

Merck Sharp & Dohme (Argentina) Inc.
José Perón
Apoderado

MERCK SHARP & DOHME ARG. INC
Farm. Sebastián Darío Goldentul
DIRECTOR TECNICO
MATRICULA NACIONAL 15436

- Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3
- Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3
- Cervical intraepithelial neoplasia (CIN) grade 1
- Vulvar intraepithelial neoplasia (VIN) grade 1
- Vaginal intraepithelial neoplasia (VaIN) grade 1.

2.5.1.4 Scientific Background

2.5.1.4.1 Public Health Burden of HPV-Related Clinical Disease

HPV infection is the most common sexually transmitted disease worldwide. Over 50% of sexually active adults become infected with HPV during their lifetime [Ref. 5.4: 1716, 1887].

HPV infection can cause pre-cancerous epithelial dysplastic lesions that can result in cancer, as well as benign tumors.

Cervical Cancer. Over 490,000 cases of cervical cancer are diagnosed worldwide annually [Ref. 5.4: 1235, 1767, 1867]. The 5-year survival averages 50 to 70% worldwide, depending on stage at diagnosis. The mortality and morbidity associated with cervical cancer is accentuated relative to other cancers because this disease generally affects women in their 30s to 50s, a period of peak family life and productivity [Ref. 5.4: 328].

Cervical cancer screening has shifted the burden of cervical HPV infection from the morbidity of cervical cancer to the management of millions of precancerous lesions. It is estimated that the lifetime risk for detection of CIN in well-screened populations approaches 25%. These lesions are divided into 3 categories based on their oncogenic potential: CIN 1, CIN 2, and CIN 3/AIS. CIN 1, or low grade dysplasia, is the most common dysplastic lesion caused by HPV infection. CIN 1 is generally understood to be a manifestation of productive HPV infection, often regresses spontaneously. CIN 3 and Adenocarcinoma *in situ* (AIS) are the immediate and obligate precursors to cervical squamous cell- and adeno-carcinoma, respectively. CIN 2 is an intermediate pathological state that includes early CIN 3 lesions and particularly dysplastic CIN 1 lesions. The standard of care in most countries is to follow women with CIN 1 lesions, reserving excision to those with whose lesions are chronic. For CIN 2/3 and AIS, the standard of care is wide excision. The success of cervical cancer screening in reducing cervical cancer rates is based on the detection and excision of CIN 2/3 and AIS lesions (Secondary Prevention).

Vulvar and Vagina Cancer. In the U.S., ~3500 women are diagnosed with HPV-related vulvar or vaginal cancers, and ~1100 women die from these cancers annually. These cancers generally occur in young women and are preceded by dysplastic lesions (vulvar intraepithelial neoplasia, or VIN, and vaginal intraepithelial neoplasia, or VaIN). VIN and VaIN lesions are classified in an analogous manner to CIN. The natural history and the clinical relevance of these lesions are also similar to those of the corresponding CIN

Merck Sharp & Dohme (Argentina) Inc.
José Peroni
Apoderado

MERCK SHARP & DOHME ARG. INC.
Farm. Sebastián Darío Goldentul
DIRECTOR TECNICO
MATRICULA NACIONAL 15436

lesions. Rates of VIN have been increasing in the United States (U.S.) and Europe, particularly among women in their 30s and 40s [Ref. 5.4: 533, 807, 1225]. VIN 2/3 and VaIN 2/3 are the immediate and obligate precursors for HPV-related vulvar and vaginal cancer.

Genital Warts. Condyloma acuminata, or genital warts, are present in approximately (~) 1% of sexually active men and women in the U.S. [Ref. 5.4: 1705, 1805]. Genital warts are benign proliferative lesions of the external anogenital tract. The incidence of genital warts in among men and women in their 20s, 30s, and 40s is substantial. Genital warts cause significant psychological and physical morbidity. Individuals who develop genital warts have a high incidence of depression, sexual dysfunction, and disruptions to long-term intimate relationships [Ref. 5.4: 496, 1821]. Anogenital warts cause pruritus and dyspareunia. Ablative therapies can achieve regression, but recurrence is common. Therapy is approximately 70% effective; thus, 30% of genital wart lesions recur. Recurrent lesions are treated with the same methods [Ref. 5.4: 827, 1984].

Recurrent Respiratory Papillomatosis (RRP). RRP is characterized by rapidly growing, histologically benign laryngeal warts. Annually, ~2300 and ~3600 cases are reported in children and adults, respectively, in the U.S. The disease causes airway obstruction. Patients must undergo frequent laser excision; some cases are fatal [Ref. 5.4: 1969].

Other Cancers. HPV infection can cause anal, penile, and certain oral cancers [Ref. 5.4: 341, 450, 1018].

2.5.1.4.2 HPV Virology and Pathophysiology of HPV Infection

The Papillomavirus family has been organized into species groupings based on the major capsid protein, L1, sequence homologies. Members of a papillomavirus species members share ~75% L1 gene sequence homology as well as a common pathophysiology. Individual types within a given HPV species may have up to 90% homology.

The 40 HPV types that infect the genital tract are classified as high-risk types that can cause cancer or low-risk types that cause dysplasia that rarely progresses to cancer [Ref. 5.4: 685]. The 18 HPV types that have been classified as being oncogenic (HPV 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, and 82) are members of 5 species [Ref. 5.4: 685]. HPV 16 is the prototype of the A9 species, which includes 6 cancer-causing HPV types (HPV 16, 31, 33, 35, 52, and 58). HPV 18 is the prototype of the A7 species, which includes 5 cancer-causing HPV types (HPV 18, 39, 45, 59, and 68) [Ref. 5.4: 685, 1022]. The remaining 3 species of oncogenic HPV types, A5 (Prototype HPV 51), A6 (Prototype HPV 56), and A11 (prototype HPV 73) rarely cause cancer but often cause CIN lesions.

HPV 16 and/or HPV 18 cause most HPV-related cancer cases. The A9 species cause (~) 70% of cervical cancers [Ref. 5.4: 685]. The A7 species cause ~20% of cervical cancers [Ref. 5.4: 685]. HPV 16 causes over 80% of HPV-related vulvar and vaginal cancers [Ref. 5.4: 2037]. HPV 6 and HPV 11 are the most common low-risk HPV types, causing >90% of genital warts and RRP [Ref. 5.4: 342, 1767, 1889].

Apoderado

MERCK SHARP & DOHME ARG. INC.
Farm. Sebastián Darío Goldentul
DIRECTOR TECNICO
MATRICULA NACIONAL 15436

2.5.1.4.3 Epidemiology of HPV Infection – Impact on Clinical Trial Design

The median age of sexual debut is ~16 years in most countries [Ref. 5.4: 824, 1091, 1124]. By 5 years after sexual debut, ~50% of young women will have been infected with at least one of the 40 genital HPV types [Ref. 5.4: 1716, 1889]. Studies suggest a similar infection pattern in men [Ref. 5.4: 744]. The peak incidence of HPV infection occurs in young adults. Hence, the efficacy of the qHPV vaccine was first evaluated in 16- to 26-year-old women (for the purpose of this Application, termed Young-Adult Women, or YAW).

The qHPV vaccine is meant to be a prophylactic vaccine, so HPV vaccination programs will include children below the age of 16. Efficacy trials in children were not conducted, as it is not feasible to collect genital samples in children. Instead, immunogenicity studies were conducted. Vaccine efficacy in 9- to 15-year-olds was inferred based on a demonstration of the robust immunogenicity of the qHPV vaccine in this age range.

Although the incidence of HPV disease peaks within 10 years of sexual debut, **women remain at risk for acquisition of HPV infection and development of clinical HPV disease throughout their sexual lives** [Ref. 5.4: 827, 1160, 1917]. Increases in the age of first marriage, rates of divorce, and infidelity over the past 30 years have further increased the risk of HPV infection among women in their late 20s, 30s, and 40s [Ref. 5.4: 2111].

A review of the literature, presented in this Application, confirms that 27- to 45-year-old women (Mid-Adult Women, or MAW) remain at substantial risk for acquisition of HPV infection and clinical HPV disease. Protocol 019 (P019) is an efficacy study of qHPV vaccine among 3819 24- to 45-year-old women. The study represents one of the largest natural history studies of HPV infection in MAW. In this study:

- At Day 1, 67% of study subjects had no evidence of past or current infection with any of the 4 vaccine HPV types;
- Among placebo subjects who were naïve to vaccine HPV types at Day 1, the incidence of persistent HPV 6, HPV 11, HPV 16, or HPV 18 infection was 2.0 per 100 person-years at risk; and
- the incidence of HPV 6-, 11-, 16-, or 18-related CIN or External Genital Lesions (EGLs) in the was 1.2 per 100 person-years at risk in all women who received placebo.

A vaccine that protects MAW from infection and disease caused by common HPV types will be a major medical advance - and fulfill a currently unmet medical need.

2.5.1.4.4 Study Endpoints in Efficacy Studies of qHPV in Women

2.5.1.4.4.1 Study Endpoints – Mid-Adult Women (24- to 45-Year-Old Women)

Context of Phase III Program in YAW. The clinical program that led to licensure of qHPV vaccine was conducted among YAW. The licensure of this vaccine was based on a definitive demonstration of the high efficacy of qHPV vaccine in preventing HPV

16/18-related CIN 2/3, AIS, VIN 2/3, and VaIN 2/3, HPV 6/11/16/18-related CIN (any grade) or AIS, and HPV 6/11-related genital warts when administered to YAW. Also, administration of qHPV vaccine or its HPV 16 vaccine prototype was shown to be highly effective in preventing the acquisition of persistent HPV 6, 11, 16, and 18 infection (of at least 6 months' duration, and of at least 12 months' duration) in this population.

Need for an Efficacy Demonstration Study in MAW. The Phase II/III clinical program for the qHPV vaccine (Protocol 005, Protocol 007, Protocol 013, and Protocol 015, or P005, P007, P013, and P015, respectively) did not evaluate 27- to 45-year-old women; only a small number of 24- to 26-year-old women were enrolled. Thus, it was necessary to conduct a study to apply the results of the program in YAW to 24- to 45-year-old women (MAW). Such a demonstration study would be based on the foundation of the extensive, definitive Phase II/Phase III efficacy program for the qHPV vaccine in YAW.

An efficacy demonstration study, rather than an immunobridging study, was required to apply the findings in YAW to MAW because the immune response in MAW was expected to be less robust than the immune response in YAW, and an immune correlate of efficacy for the qHPV vaccine had not been defined.

Endpoints for the Efficacy Study in MAW. The proper endpoint for an efficacy demonstration study to permit the application of findings in YAW to MAW was chosen on the basis of the natural history of HPV disease and the breadth, depth, and results of the clinical program for qHPV vaccine in YAW:

- **Natural History.** Persistent HPV 6, 11, 16, and 18 infections are a necessary prerequisite for each of the HPV 6-, 11-, 16-, and 18-related clinical endpoints evaluated in the Phase II/Phase III program in YAW. The placebo arms of the Phase II/Phase III program for the qHPV vaccine have demonstrated the strong correlation between persistent infection and development of clinical disease.
- **Results of the Phase II and Phase III Program in YAW.** The Phase II/III clinical program for the qHPV vaccine in YAW has definitively demonstrated the high, durable prophylactic efficacy of the vaccine with respect to HPV 16- and 18-related CIN 3, AIS, VIN 2/3 and VaIN 2/3, HPV 6-, 11-, 16-, or 18-related CIN 1, and HPV 6- and HPV 11-related condyloma acuminata. Administration of qHPV vaccine was equally efficacious with respect to persistent HPV 6, 11, 16, or 18 infections.
- The likelihood ratios (LR) for persistent infection producing clinical disease for the EOS data for both high-risk HPV types and low-risk HPV types confirm that persistent infection of 6 months duration is the appropriate metric for this efficacy bridge (see [Appendix 2.5: 1] and [Appendix 2.5: 2]).

Based on these factors, the composite endpoint for the Efficacy Demonstration Study of the qHPV vaccine in MAW (P019) consisted of persistent infection, CIN, or EGL caused by vaccine HPV types. Inclusion of persistent infection in this endpoint was justified by (1) the size and results of the clinical trials of qHPV vaccine in YAW; (2) the central role of persistent infection in the pathogenesis of HPV-related cervical, vulvar, and vaginal

disease; and (3) the consistent efficacy of the qHPV vaccine with respect to persistent infection and to cervical, vulvar, and vaginal disease caused by vaccine HPV types.

2.5.1.4.4.2 Other Important Endpoints

2.5.1.4.4.2.1 Overall Impact of Vaccination – Disease Cause by Vaccine or Non-Vaccine HPV Types

The public health impact of a prophylactic HPV vaccine will be measured by its impact on the overall rates of cervical, vulvar, and vaginal disease (caused by vaccine and non-vaccine HPV types). Such analyses are also important to physicians and to populations for which the vaccine is indicated, as they address whether vaccination will reduce individual subjects' overall risk for development of cervical, vulvar, and vaginal cancer, as well as the precancerous lesions that precede them.

2.5.1.5 Overview: Clinical Development Program for qHPV Vaccine

Studies in Young Adult Women and Adolescents. The clinical development program for qHPV vaccine initially targeted 9- to 26-year-old girls and women and 9- to 15-year-old boys. This range covers the period just prior to sexual debut through the period of peak risk for HPV infection.

The clinical program for qHPV vaccine was designed to measure the impact of the vaccine on cervical cancer risk using a composite endpoint of CIN 2/3, AIS, and cervical cancer. Subjects in these studies were followed for an average of ~3.5 years post-vaccination. The Application presents updated results regarding efficacy of the qHPV vaccine with respect to (1) HPV 16- or HPV 18-related cervical, vulvar, and vaginal cancer (using surrogate markers); (2) the duration of efficacy; (3) cross-protection efficacy; (4) the theoretical risk of HPV type replacement; (5) the overall risk for development of cervical, vulvar, and vaginal cancer (caused by vaccine or non-vaccine HPV types) (using surrogate markers); and (6) the overall risk for development of cervical, vulvar, or vaginal precancerous lesions (caused by vaccine or non-vaccine HPV types).

Studies in Young Adult Men. Studies in men 16 to 26 years of age are in progress.

Studies in Mid-Adult Women. P019 is the efficacy demonstration study of qHPV vaccine in 24- to 45-year-old women. The efficacy objectives of P019 are:

- Primary Efficacy Objectives: (a) To demonstrate that administration of qHPV vaccine reduces the combined incidence of HPV 6/11/16/18-related persistent infection, genital warts, VIN, VaIN, vulvar cancer, vaginal cancer, CIN, AIS, and cervical cancer, compared with placebo in 24- to 45-year-old women who are naïve to the relevant HPV type at baseline; and (b) To demonstrate that administration of qHPV vaccine reduces the combined incidence of HPV 16/18-related persistent infection, genital warts, VIN, VaIN, vulvar cancer, vaginal cancer, CIN, AIS, and cervical cancer, compared with placebo in 24- to 45-year-old women who are naïve to the relevant HPV type at baseline.

Merck Sharp & Dohme (Argentina) Inc.
José [illegible]
Apoderado

MERCK SHARP & DOHME ARG. INC
Farm. Sebastián Darío Goldentul
DIRECTOR TECNICO
MATRICULA NACIONAL 15436

- Secondary Efficacy Objectives: (a) To demonstrate that administration of qHPV vaccine reduces the combined incidence of HPV 6/11-related persistent infection, genital warts, VIN, VaIN, vulvar cancer, vaginal cancer, CIN, AIS, and cervical cancer, compared with placebo in 24- to 45-year-old women who are naïve to the relevant HPV type at baseline; and (b) To demonstrate that administration of qHPV vaccine reduces the combined incidence of HPV 31/33/35/52/58-related persistent infection, genital warts, Vulvar Intraepithelial Neoplasia (VIN), Vaginal Intraepithelial Neoplasia (VaIN), vulvar cancer, vaginal cancer, cervical dysplasia (any grade Cervical Intraepithelial Neoplasia [CIN]), cervical Adenocarcinoma in Situ (AIS), and cervical cancer, compared with placebo in 24- to 45-year-old women who are naïve to the relevant HPV type at baseline.
- Tertiary Efficacy Objective: To demonstrate that administration of qHPV vaccine reduces the combined incidence of the following Pap diagnoses related to HPV 16 and/or 18 compared with placebo in 24- to 45-year-old women who are naïve to the relevant HPV type at baseline: atypical squamous cells of undetermined significance (ASC-US) with positive high-risk probe, low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesions (HSIL), atypical squamous cells, cannot exclude HSIL (ASC-H), atypical glandular cells (AGC), and cancer.

An endpoint-driven analysis of P019 was conducted when at least 25 subjects in the primary efficacy population developed a case of HPV 6-, 11-, 16-, or 18-related persistent infection or cervical, vulvar or vaginal disease, and at least 14 subjects in the primary efficacy population developed a case of HPV 16- or 18-related persistent infection or cervical, vulvar, or vaginal disease. The required number of cases was accrued in visits conducted as of 13-Jul-2007. Additionally, the required number of HPV 6- and 11-related cases (secondary objective) had also been accrued.

2.5.1.6 Standard Research Procedures

The study methodology, subject selection, selection of endpoints, immunologic assays, and assessment of safety were in accordance with the established practices for conducting vaccine studies. P019 included the following standard procedures: (1) Subjects were enrolled regardless of Day 1 HPV status or Pap test results. (2) Subjects were referred to colposcopy according to mandatory Pap test triage algorithms. (3) Subjects underwent detailed genital inspection to ensure full ascertainment of lesions (identical to P013). (4) The Phase III program central laboratory processed and provided diagnoses for all ThinPrep™ (Cytyc, Boxborough MA, U.S.A.) Pap Tests and all tissue specimens for the purposes of medical management. (5) All tissue specimens were read by the Phase III Pathology Panel (See sections 6 and 9.1.3.5 in [Ref. 5.3.5.1: P019]) to provide a final diagnosis for study purposes. The Panel was blinded to the diagnosis of the Program Central Laboratory and all HPV testing results. (6) Tissue specimens were sent to Merck and PPD Vaccine and Biologics Laboratory for HPV testing. All specimens (regardless of histologic diagnosis) were tested by PCR for HPV to determine the causal HPV type in the lesion. (7) Immunogenicity assays measured neutralizing serum anti-HPV. And (8)

Jose [illegible]
Apoderado

MERCK SHARP & DOHME ARG. INC
Farm. Sebastian Dario Goldentul
DIRECTOR TECNICO
MATRICULA NACIONAL 15436

qHPV vaccine was evaluated for: (a) injection-site and systemic tolerability; (b) impact on long-term health status; and (c) interaction with pregnancy and lactation, events that are likely to occur in the target population for which qHPV vaccine is indicated. All study procedures used in P019 have been used in the Protocols submitted in prior Applications.

Statistical Analyses. Statistical analyses for P019 was prespecified in the Statistical Analysis Plan (SAP) [Ref. 5.4: 3159] and included in the clinical study report (CSR) [Ref. 5.3.5.1: P019]. All analyses were performed using standardized and validated methods.

2.5.1.7 Regulatory Guidance and Advice

As of 01-Nov-2009, the qHPV vaccine has been licensed in 117 countries.

2.5.1.8 Good Clinical Practices

The clinical trials were conducted in accordance with current standard research approaches with regard to the design, conduct, and analysis of such trials including the archiving of essential documents. All trials were conducted following appropriate Good Clinical Practice guidelines and considerations for the ethical treatment of human subjects that were in place at the time the trials were performed.

2.5.2 Overview of Biopharmaceutics

No traditional biopharmaceutic studies were conducted in support of this supplemental Application, as such studies are not applicable to vaccines. Quadrivalent HPV vaccine is an injectable recombinant vaccine that is immediately bioavailable. The bioavailability of the vaccine is confirmed by the development of serum anti-HPV responses to the component L1 VLP types.

2.5.3 Overview of Clinical Pharmacology

No clinical pharmacology studies of qHPV vaccine were conducted in support of this Application. Such studies are not routinely conducted as part of the evaluation of vaccines. As stated in Section 3.2.1 of the CPMP "Note for Guidance on Clinical Evaluation of New Vaccines," 19-May-1999 (CPMP/EWP/463\97), pharmacokinetic and pharmacodynamic studies are generally not required for injectable vaccines because they do not provide useful information for establishing adequate dosing recommendations.

2.5.4 Overview of Efficacy and Immunogenicity

Studies contributing additional data to the evaluation of the efficacy and immunogenicity of qHPV vaccine are summarized in [Appendix 2.5: 1].

2.5.4.1 Clinical Efficacy

The efficacy results presented here are the end-of-study (EOS) results for qHPV in P019 (MAW).

Efficacy endpoints were evaluated in predefined populations (see [Appendix 2.5: 3] and [Appendix 2.5: 4]). The Per-Protocol Efficacy (PPE) population was the primary

efficacy analysis population. Prophylactic efficacy was also evaluated in a broader population of subjects termed the HPV-Naïve to the Relevant HPV Type (HNRT) population.

Analyses were conducted to evaluate the impact of the qHPV on the burden of HPV infection and related disease in the general study population. These analyses were conducted in the Full Analysis Set (FAS) population. This population included subjects who: (1) received at least one vaccination and (2) had at least one follow-up visit after 1 day following the first injection.

2.5.4.1.1 Program in Mid-Adult Women (MAW)

2.5.4.1.1.1 Overview – Protocol 019

Protocol 019 was designed to demonstrate the efficacy, immunogenicity, and safety of qHPV vaccine in women 24- to 45-years of age.

2.5.4.1.1.2 Subject Disposition and Subject Accounting

The median follow-up time of 4.0 years per study participant (mean follow-up time was 3.8 years). A total of 89.7% and 88.6% of study subjects completed their Month 36 and Month 48 visits, respectively.

The primary efficacy analysis was conducted in the PPE population. Among the 3819 subjects enrolled in the study, 69.6%, 70.1%, and 79.6% were eligible for the PPE analysis related to HPV types 6/11, 16, and 18, respectively. The most common reasons for exclusion of subjects from participation in the relevant PPE populations were detection of DNA for the relevant HPV type in cervicovaginal specimens obtained at Day 1 or Month 7, and detection of relevant anti-HPV responses in sera obtained at Day 1.

Analyses of efficacy in the HNRT and the FAS populations were also conducted.

2.5.4.1.1.3 Enrollment Characteristics

Subjects were enrolled in 2 approximately equal age strata (24- to 34-year-olds and 35- to 45-year-olds). Approximately 67% of study subjects were seronegative and PCR negative for HPV 6, 11, 16 and 18 at Day 1 and were, therefore, susceptible to infection with any of the 4 vaccine HPV types [Appendix 2.5: 5]. Among women who were positive to at least 1 vaccine HPV type, 71.1% were positive to exactly 1 vaccine HPV type.

2.5.4.1.1.4 Efficacy Results – Protocol 019 (MAW)

Summary:

- The EOS findings confirm the efficacy of the qHPV vaccine in adult women in the PPE population demonstrated in the 2007 endpoint-driven analysis for the protocol-defined primary analysis population, against the protocol-defined co-primary and secondary efficacy endpoints (see [Table 2.7.3-cervixcancer: 9] and [Table 2.7.3-exgenlesion: 8]). There were no new cases of HPV 6/11/16/18-related CIN or EGL reported in the qHPV group in the PPE population since the 2007 endpoint-driven analysis (see [Table 2.7.3-cervixcancer: 3] and [Table 2.7.3-exgenlesion: 3]); in

contrast there were 8 new cases of HPV 6/11/16/18-related CIN (any grade), 2 new cases of HPV 6/11/16/18-related CIN 2/3 or worse, and 3 new cases of EGL in the placebo group of the PPE population during the same time period.

- In the PPE analysis population and in the FAS analysis population, the estimate of efficacy of the qHPV vaccine against the HPV 16/18-related CIN (any grade) endpoint is nominally statistically significant at EOS, while not so in the 2007 endpoint-driven analysis (see [Table 2.7.3-cervixcancer: 5] and [Table 2.7.3-exgenlesion: 5]).

- In the PPE analysis population, the estimates of efficacy of the qHPV vaccine against the HPV 6/11-related genital warts (condyloma) endpoint, as well as against the CIN (any grade) endpoint, are nominally statistically significant at EOS (while not so at the time of the 2007 endpoint-driven analysis) (see [Table 2.7.3-cervixcancer: 5] and [Table 2.7.3-exgenlesion: 5]).

- [Appendix 2.5: 6] shows that efficacy by region in the primary analysis population was very similar. In North America efficacy was 91.1%, in Europe efficacy was 88.8%, in Latin America it was 84.7% and in Asia-Pacific efficacy was 100.0%. Additionally, the proportion of women who are the PPE population in each region is quite similar. In North America and Europe, the PPE population makes up approximately 80% of the FAS population and in Latin America and Asia-Pacific, the proportion is approximately 86%.

- In the seropositive and PCR negative population, efficacy was 66.8%, which is statistically significant against re-acquisition or recurrent persistent infection in the population 24 to 45 years of age overall (see [Table 2.7.3-cervixcancer: 47] and [Table 2.7.3-exgenlesion: 22]).

- At EOS the efficacy of the qHPV vaccine against the HPV 6/11/16/18-, or the HPV 16/18-related CIN 2/3 or worse endpoint was improved relative to the 2007 endpoint-driven analysis in the PPE, HNRT, and FAS analysis populations (see [Table 2.7.3-cervixcancer: 3], [Table 2.7.3-exgenlesion: 3], [Table 2.7.3-cervixcancer: 5], and [Table 2.7.3-exgenlesion: 5]). There were no new cases of HPV 16/18-related CIN 2/3 or worse in the qHPV vaccine group in either the PPE or HNRT populations since the 2007 endpoint-driven analysis (see [Table 2.7.3-cervixcancer: 5] and [Table 2.7.3-exgenlesion: 5]).

- In the FAS analysis population, the efficacy of the qHPV vaccine against HPV 6/11/16/18- or HPV 16/18- related persistent infection, CIN (including CIN 2/3 or worse), and EGL improved relative to the 2007 endpoint-driven analysis (see [Table 2.7.3-cervixcancer: 3], [Table 2.7.3-exgenlesion: 3], [Table 2.7.3-cervixcancer: 5], and [Table 2.7.3-exgenlesion: 5]); there were substantively more cases of each endpoint in the placebo group than in the qHPV vaccine group since the 2007 endpoint-driven analysis.

- In the FAS analysis population, VE against any CIN 2/3 or worse (regardless of HPV-type) also improved relative to the 2007 endpoint-driven analysis (see [Table 2.7.3-cervixcancer: 8]). Specifically, there were 25 new cases of CIN 2/3 or worse (qHPV = 10, Placebo = 15) since the 2007 endpoint-driven analysis, and of these, the number of cases due to non-qHPV-types tested (i.e. HPV 31/33/35/39/45/51/52/56/58/59), and similarly for cases not related to any of the 14 tested HPV types, were approximately equally distributed between the qHPV and the placebo groups. These data indicate that there has been no imbalance in acquisition of non-qHPV type CIN 2/3 or worse since the 2007 endpoint-driven analysis.

- In the PPE population, the results of analysis of efficacy against HPV 6/11/16/18-related persistent infection are similar to the results of analysis of efficacy against the composite HPV 6/11/16/18-related persistent infection and disease endpoints (compare [Table 2.7.3-cervixcancer: 14] with [Table 2.7.3-cervixcancer: 9] and [Table 2.7.3-exgenlesion: 8]). In addition, results of an exploratory analysis of efficacy against HPV16/18-related persistent infection in the PPE population based on a duration of ≥12 months showed a similar VE to the protocol defined definition of ≥6 months (±1 month) (see [Table 2.7.3-cervixcancer: 15]).

- In the cohort of women who were PCR positive and seronegative at Day 1 for HPV 16, an imbalance in non-vaccine HPV type co-infections between the qHPV vaccine group and the placebo group potentially explains the higher persistence of HPV type 16 in the qHPV-vaccinated group compared to placebo recipients. In the qHPV-vaccinated group, 15 of the 21 subjects who did not clear their Day 1 HPV 16-related infection had co-infections, compared to 7 of the 11 placebo recipients who did not clear their Day 1 HPV 16-related infection who had co-infections (see [Appendix 2.5: 7]). These 15 qHPV-vaccinated subjects and 7 placebo recipients who did not clear their Day 1 HPV 16-related infection and had co-infections represent 37% (15 of 41) and 16% (7 of 43) of all qHPV-vaccinated subjects and placebo recipients, respectively, who were HPV 16-infected at Day 1. Additionally, an HPV type 16 time-to-clearance (life-table) analysis of women with and without co-infection shows that co-infection is responsible for the delayed clearance observed in the vaccine group [Appendix 2.5: 8].

HPV 6/11/16/18-related Persistent Infection and Disease Endpoints

[Table 2.7.3-cervixcancer: 9] and [Table 2.7.3-exgenlesion: 8] presents the estimates of VE against HPV 6/11/16/18-related persistent infection and disease endpoints in the stratified analysis by age and by HPV type in all ages based on the full EOS data. Overall VE is 88.7% (95% CI 78.1, 94.8) and is similar across both age strata, HPV types 16/18 and HPV types 6/11, as well as for each HPV type individually. [Appendix 2.5: 9] presents the data with regard to specific endpoints and demonstrates that the point estimate of efficacy against CIN2/3+ due to vaccine types is high in all analysis populations.

[Table 2.7.3-cervixcancer: 3] and [Table 2.7.3-exgenlesion: 3] presents the estimates of VE against HPV 6/11/16/18-related persistent infection and disease endpoints in the PPE, HNRT, and FAS analysis populations based on the full EOS data. For the composite endpoint of HPV 6/11/16/18-related persistent infection, CIN and EGL, the estimate of VE is statistically significant at the nominal 0.05 level of significance in each of the PPE, HNRT, and FAS analysis populations. Similar statistical significance were observed in all 3 analysis populations individually for the HPV 6/11/16/18-related persistent infection endpoint and for the HPV 6/11/16/18-related CIN (any grade) endpoint. The point estimate of efficacy against persistent infection is slightly lower at EOS compared to the estimate at the time of the 2007 endpoint-driven analysis. Nominally statistically significant results were observed for HPV 6/11/16/18-related EGL (condyloma) endpoint in the PPE and HNRT analysis populations at EOS. [Figure 2.7.3-cervixcancer: 1] and [Figure 2.7.3-exgenlesion: 1] shows graphically that in the HNRT population (naïve at baseline) new cases of persistent infection, CIN and EGL continue to accrue in the placebo group and that new cases are do not occur after the initial prevalent cases become manifest.

[Table 2.7.3-cervixcancer: 3] and [Table 2.7.3-exgenlesion: 3] presents the comparison of VE estimates based on the 2007 endpoint-driven analysis and based on the analysis of the EOS data.

- In the FAS, the estimate of efficacy of the qHPV vaccine against the HPV 6/11/16/18-related CIN (any grade) endpoint is nominally statistically significant at EOS (while not so in the endpoint-driven analysis conducted in 2007).
- In each of the PPE, HNRT, and FAS analysis populations, the estimate of efficacy of the qHPV vaccine against the HPV 6/11/16/18-related CIN 2/3 or worse endpoint is higher at EOS compared to the estimate based on the 2007 endpoint-driven analysis.
- There were a total of 48 (qHPV = 21, placebo = 27) cases of HPV 6/11/16/18-related CIN 2/3 or worse at EOS in the FAS analysis population (see [Table 2.7.3-cervixcancer: 3] and [Table 2.7.3-exgenlesion: 3]).

HPV 16/18-related Persistent Infection and Disease Endpoints

[Table 2.7.3-cervixcancer: 4] and [Table 2.7.3-exgenlesion: 4] presents the estimates of VE against HPV 16/18-related persistent infection and disease endpoints in the PPE, HNRT, and FAS analysis populations based on the full EOS data. [Table 2.7.3-cervixcancer: 5] and [Table 2.7.3-exgenlesion: 5] presents the comparison of VE estimates based on the 2007 endpoint-driven analysis and based on the analysis of the EOS data.

- In the PPE analysis population and in the FAS analysis population, the estimate of efficacy of the qHPV vaccine against the HPV 16/18-related CIN (any grade) endpoint is nominally statistically significant at EOS, while not so

Merck Sharp & Dohme (Argentina) Inc.
Jose Nerone
Apoderado

MERCK SHARP & DOHME (ARG.) INC.
Farm. Sebastian Dario Goldszer
DIRECTOR TECNICO
MATRICULA NACIONAL 15439

in the 2007 endpoint-driven analysis (see [Table 2.7.3-cervixcancer: 5] and [Table 2.7.3-exgenlesion: 5]).

- In each of the PPE, HNRT, and FAS analysis populations, the estimate of efficacy of the qHPV vaccine against HPV 16/18-related CIN 2/3 or worse endpoint is higher at EOS compared to the estimate at the time of the 2007 endpoint-driven analysis.
- The EOS data also demonstrate the value of HPV 16/18-related persistent infection as a predictor of subsequent progression to HPV 16/18-related CIN2/3+. The estimate of the likelihood ratio positive (LR+) statistic in an evaluation of the value of HPV 16/18-related persistent infection as a predictor of subsequent progression to HPV 16/18-related CIN2/3+ is 20.1 (95% CI: 14.3, 28.3). In published literature, a value of LR+ ≥10.0 is an acceptable evidence that a positive value of a "diagnostic test" (e.g., positive for HPV 16/18-related persistent infection) has a good predictive value for also being positive on a "gold standard test" (e.g., positive for HPV 16/18-related CIN2/3+) [Appendix 2.5: 10].

HPV 6/11-related Persistent Infection and Disease Endpoints

[Table 2.7.3-cervixcancer: 6] and [Table 2.7.3-exgenlesion: 6] presents the estimates of VE against HPV 6/11-related persistent infection and disease endpoints in the PPE, HNRT, and FAS analysis populations based on the full EOS data.

[Table 2.7.3-cervixcancer: 7] and [Table 2.7.3-exgenlesion: 7] presents the comparison of VE estimates based on the 2007 endpoint-driven analysis and based on the analysis of the EOS data.

- In the PPE analysis population, the estimates of efficacy of the qHPV vaccine against the HPV 6/11-related genital warts (condyloma) endpoint, as well as against the CIN (any grade) endpoint, are nominally statistically significant at EOS (while not so at the time of the 2007 endpoint-driven analysis) (see [Table 2.7.3-cervixcancer: 5] and [Table 2.7.3-exgenlesion: 5]).
- In the HNRT analysis population, the estimate of efficacy of the qHPV vaccine against the HPV 6/11-related genital warts endpoint was nominally statistically significant at the time of the 2007 endpoint-driven analysis, and that result persisted through EOS (see [Table 2.7.3-cervixcancer: 5] and [Table 2.7.3-exgenlesion: 5])

The EOS data demonstrate the efficacy of the qHPV vaccine (in the PPE and HNRT populations) against HPV 6/11-related genital warts. Furthermore, the EOS data also demonstrate the value of HPV 6/11-related persistent infection as a predictor of subsequent progression to HPV 6/11-related genital warts (as described above for HPV 16/18 persistent infection and CIN2/3+). The estimate of the likelihood ratio positive (LR+) statistic in an evaluation of the value of HPV 6/11-related persistent infection as a predictor of subsequent progression to HPV 6/11-related genital warts is 37.2 (95% CI:

27.4, 50.4). In published literature, a value of LR+ ≥10.0 is an acceptable evidence that a positive value of a "diagnostic test" (e.g., positive for HPV 6/11-related persistent infection) has a good predictive value for also being positive on a "gold standard test" (e.g., positive for HPV 6/11-related genital warts) [Appendix 2.5: 10].

CIN 2/3 or Worse Due to Any HPV Type in the FAS

[Table 2.7.3-cervixcancer: 8] presents the comparison of VE estimate against the CIN 2/3 or worse due any HPV type endpoint in the FAS analysis population based on the 2007 endpoint-driven analysis and based on the analysis of the EOS data.

- At the time of the 2007 endpoint-driven analysis, there were 88 (qHPV = 52, placebo = 36) cases of CIN 2/3 or worse due to any HPV type in the FAS.
- At EOS, there were 113 (qHPV = 62, placebo = 51) cases of CIN 2/3 or worse due to any HPV type in the FAS.
- The higher number of cases of CIN 2/3 or worse due to any HPV type observed in the qHPV vaccine group compared to placebo were attributable to CIN 2/3 or worse cases related to non-vaccine HPV types, many of which were subjects who had confounding co-infections of high-risk HPV types Day 1, and the CIN 2/3 endpoint occurred during the first 2 years of the study (i.e., observed at the time period of Day 1 through the time of the 2007 endpoint-driven analysis).
- Similar number of non-vaccine HPV type-related CIN 2/3 or worse cases were observed in the qHPV vaccine and placebo groups (qHPV = 6, placebo = 6) during additional follow-up from the 2007 endpoint-driven analysis through the EOS.

HPV 6/11/16/18-related Persistent Infection, by Duration of Infection

[Table 2.7.3-cervixcancer: 14] shows the results of analysis of efficacy against HPV 6/11/16/18-related persistent infection in the PPE population.

- Results of analysis of efficacy against HPV 6/11/16/18-related persistent infection are similar to the results of analysis of efficacy against the composite HPV 6/11/16/18-related persistent infection and disease endpoint.
- Most of the persistent infection endpoints in the qHPV vaccine group were HPV 16-related.

[Table 2.7.3-cervixcancer: 15] shows the results of exploratory analysis of efficacy against HPV 16/18-related persistent infection in the PPE population using different definitions for the duration of infection.

- The estimate of VE against HPV 16/18-related persistent infection of ≥12 months duration was similar to the estimate of VE against persistent infection based on the protocol defined duration of ≥6 months (±1 month).

Merck Sharp & Dohme (Argentina) Inc.
Jose Perone
Apoderado

MERCK SHARP & DOHME ARG. IN
Farm. Sebastian Dario Goldent
DIRECTOR TECNICO
MATRICULA NACIONAL 15436

Reactivation of Infection and Acquisition of Disease Related to Vaccine HPV Types Among Subjects Seropositive and PCR Negative to the Relevant HPV Type

[Table 2.7.3-cervixcancer: 47] and [Table 2.7.3-exgenlesion: 22] shows the results of analysis of efficacy against HPV 6/11/16/18-related persistent infection and disease among subjects seropositive and PCR negative to the relevant HPV type at Day 1.

- The estimate of VE at EOS against HPV 6/11/16/18-related persistent infection that is of ≥6 months duration over consecutive visits 6 (±1) months apart among subjects who were seropositive and PCR-negative to the relevant HPV type at Day 1 is 66.8% (95% CI: 3.8, 90.5). Among the 35 to 45 year-old seropositive and PCR-negative subjects, the estimate of VE is 81.3% (95% CI: 14.4, 98.0).
- In a sensitivity analysis that defined persistent infection as that which is of ≥12 months duration over consecutive visits 6 (±1) months apart, the estimate of VE against HPV 6/11/16/18-related persistent infection among subjects who were seropositive and PCR-negative to the relevant HPV type at Day 1 is 33.0% (95% CI: –182.7, 86.1). Among the 35 to 45 year-old seropositive and PCR-negative subjects, the estimate of VE is 58.4% (95% CI: –154.1, 96.0).
- There were no cases of HPV 6/11/16/18-related CIN (any grade) or EGL observed among subjects who were seropositive and PCR-negative to the relevant HPV type at Day 1 during the course of the study. However, in young women, efficacy against CIN of any grade and EGL was seen and was statistically significant. The case counts for CIN was 7 in the placebo group and 0 in the qHPV vaccine group, vaccine efficacy 100% (95% CI 28.7, 100). For EGL, the counts were 8 to 0, resulting in statistically significant efficacy of 100% (95% CI 39.5, 100). Overall, efficacy was 100% (95% CI 68.9, 100) for both lesions together, [Appendix 2.5: 11].
- Analysis of women aged 16 to 45 years of age for efficacy against recurrent HPV type 16 or 18 persistent infection shows significant protection against persistent infection due to these recurrent HPV types. Efficacy against the combined HPV 16 or 18 persistent infection endpoint across all ages was 68.2% (95% CI 17.9, 89.5), [Appendix 2.5: 12].
- Analysis of efficacy against lesions in young women, [Appendix 2.5: 13], shows that statistically significant efficacy was demonstrated for both CIN and EGL of any grade (as shown above), but also was achieved for genital warts and high grade lesions, CIN2/3+, VIN2/3+ and VaIN2/3+, 100% (95% CI 62.8, 100).

Therefore, vaccination with the qHPV vaccine is associated with a lower incidence of reactivation of persistent infection related to vaccine HPV types, which is consistent with and similar to data from the efficacy studies in young women that show efficacy against both CIN and EGL, as well as persistent infection.

Merck Sharp & Dohme (Argentina) Inc.
José Arroin
Apoderado

MERCK SHARP & DOHME ARG. Inc.
Farm. Sebastián Darío Goldentul
DIRECTOR TECNICO
MATRICULA NACIONAL 15436

Clearance of HPV 16 in PCR Positive Seronegative at Day 1 Subgroup

In a recent publication (Trottier et al., JID 2008 [Ref. 5.4: 2945]), it was shown that the duration of HPV 16-related infection tends to be prolonged when co-infected with other high-risk HPV types. Our findings confirm those of Trottier, et al. A subgroup analysis relating to clearance of qHPV-vaccine-type related infection among subjects so infected at Day 1 was conducted at the time of the 2007 endpoint-driven analysis. At the time of the 2007 endpoint-driven analysis, it was noted that the clearance of HPV 16-related infection among Day 1 HPV 16-PCR positive and -seronegative qHPV-vaccinated subjects was lower (not statistically significant) compared to the clearance of HPV 16 infection among similarly Day 1 HPV 16-PCR positive and -seronegative placebo recipients.

- Analyses conducted at the EOS in this subgroup of Day 1 HPV 16-PCR positive and -seronegative subjects demonstrate findings relating to clearance of HPV 16 infection that are similar to that seen at the 2007 endpoint-driven analysis [Table 2.7.3-cervixcancer: 45].
- Exploratory examination of the characteristics of subjects who did not clear their Day 1 HPV 16 infection showed that there is an imbalance of non-vaccine HPV type co-infections (either at Day 1 or post-Day 1) between the qHPV vaccine group and the placebo group that potentially explains the higher persistence of HPV 16-related infection in the qHPV-vaccinated group compared to placebo recipients. In the qHPV-vaccinated group, 15 (37% of the qHPV vaccine group) of 21 subjects who did not clear their Day 1 HPV 16-related infection had co-infections (either at Day 1 or post-Day 1), compared to 7 (16% of the placebo group) of 11 in the placebo recipients who did not clear their Day 1 HPV 16-related infection who had co-infections (see [Appendix 2.5: 7]). This observation is a likely explanation of the lower rate of clearance of HPV 16-related infection in the qHPV vaccine group (23.4 per 100 person-years) compared to the rate of clearance in the placebo group (51.9 per 100 person-years).
- An analysis of subjects in Protocol 019 was performed using a life-table approach and is presented in
- Appendix 2.5: 8] and described below:
  - In the top half of
  - Appendix 2.5: 8], it can be seen that among subjects without high-risk HPV type co-infections, there is no difference between qHPV and placebo groups with respect to cumulative clearance-event distribution.
  - In the bottom half of
  - Appendix 2.5: 8], subjects with high-risk HPV type co-infections from 0 to 18 months show no difference between qHPV and placebo groups

with respect to the cumulative clearance-event distribution. In both groups, most of the clearance events occurred early.

- The lone driver of the "difference" between the qHPV and placebo groups is two time intervals:
  - 18 to 24 months, where 4 clearance events occurred in placebo and 0 in the qHPV vaccine group, and
  - 24 to 30 months, where 3 clearance events occurred in placebo and 1 in qHPV vaccine group,

Both intervals, coupled with the already very small at-risk set (sample size) during the 2 time intervals, are driving the "difference" between the 2 groups. The cumulative percent in the placebo group at the 24 to 30 month interval jumps to 87% from 74% during the previous time interval because the at-risk set is only 6 at the 24 to 30 month interval.

The analyses presented from the study population, as well as the published literature on relationship of co-infection and persistence of HPV infection, demonstrate that any delayed clearance that may be observed in the qHPV group is due to factors that are unrelated to vaccination.

2.5.4.1.1.5 Efficacy Conclusions – Protocol 019

With respect to Protocol 019:

- Prophylactic administration of a 3-dose regimen of qHPV vaccine to 24- to 45-year-old women is highly efficacious in preventing the development of persistent infection, CIN and EGL caused by HPV 6, HPV 11, HPV 16 or HPV 18.

- Prophylactic administration of a 3-dose regimen of qHPV vaccine to 24- to 45-year-old women is highly efficacious in preventing the development of persistent infection, CIN and EGL caused by HPV 16 or HPV 18, including persistent infection of 12 months or more.

- Prophylactic administration of a 3-dose regimen of qHPV vaccine to 24- to 45-year-old women is highly efficacious in preventing the development of persistent infection, CIN and EGL caused by HPV 6 or HPV 11.

- Prophylactic administration of a 3-dose regimen of qHPV vaccine to 24- to 45-year-old women is highly efficacious in preventing the development of CIN (any grade) or AIS caused by HPV 6, HPV 11, HPV 16 or HPV 18.

- Prophylactic administration of a 3-dose regimen of qHPV vaccine to 24- to 45-year-old women is highly efficacious in preventing the development of CIN (any grade) or AIS caused by HPV 16 or HPV 18.

- Prophylactic administration of a 3-dose regimen of qHPV vaccine to 24- to 45-year-old women is highly efficacious in preventing the development of ASCUS (HR probe positive) or worse of due to HPV types 16 or 18.

- Administration of a 3-dose regimen of qHPV vaccine to 24- to 45-year-old women protects against recurrent type-specific persistent infection in seropositive and PCR negative women.

- Vaccinated women who become pregnant transfer HPV type-specific neutralizing antibody via the placenta to their offspring.

- There is no imbalance in new onset of non-qHPV type CIN 2/3 or worse since the original event-driven analysis in 2007. This indicates that the original CIN 2/3 disparity was due to the imbalance of prevalent infection and disease observed at baseline between the qHPV vaccine and placebo groups.

- In HPV type 16 PCR positive, seronegative women at Day 1, the imbalance of non-vaccine type co-infection between the qHPV vaccine group and the placebo group explains the slower clearance of HPV 16 in vaccinated women infected with HPV type 16 at baseline.

2.5.4.2 Immunogenicity

Preclinical studies with L1 VLP vaccines demonstrated that: (1) administration of L1 VLP vaccines protected animals from species-specific papillomavirus infection; (2) this protective efficacy was associated with virus-neutralizing immune responses; and (3) unvaccinated animals that were given serum from vaccinated animals became protected from infection/disease. These results supported the hypothesis that induction of systemic anti-HPV responses HPV L1 VLP vaccine should result in protection against HPV infection or disease [Ref. 5.4: 327, 1929, 2010]. Based on the results of the preclinical studies, the clinical program has utilized vaccine type-specific anti-HPV serum levels as the primary means to measure the immunogenicity of the HPV L1 VLP vaccines.

The minimal anti-HPV response that provides protection against HPV infection and disease is not known for the following reasons: (1) the dependence of the HPV viral life cycle on terminal differentiation of epithelial cells has precluded the development of functional assays to demonstrate that vaccine-induced anti-HPV responses can neutralize live virions; and (2) the high efficacy of the qHPV vaccine means that it has not been possible to correlate vaccine failure with vaccine-induced anti-HPV levels.

2.5.4.2.1 Protocol 019: Phase III Study of qHPV vaccine in 24- to 45-Year Old Women (Mid-Adult Women, or MAW)

P019 [Ref. 5.3.5.1: P019] had the following immunogenicity objectives: (1) To evaluate the kinetics and age dependence of anti-HPV 6, 11, 16, and 18 responses following administration of a 3-dose regimen of qHPV vaccine; and (2) To observationally compare

Merck Sharp & Dohme (Argentina) Inc.

MERCK SHARP & DOHME ARG. INC.
Farm. Sebastián Darío Goldentul
DIRECTOR TECNICO
MATRICULA NACIONAL 15436

anti-HPV 6, 11, 16, and 18 responses following administration of a 3-dose regimen of qHPV vaccine among HPV-naïve women 24 to 45 years of age enrolled in this protocol. The study enrolled a total of 3819 subjects in 2 equal age strata (24- to 34-year-olds and 35- to 45-year-olds). All subjects were to undergo serology testing for anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 levels at Day 1, and Months 7, 12, 24, 36, and 48. The primary immunogenicity evaluations were to be conducted in the PPI population.

Anti-HPV GMTs at Month 7

As previously shown, administration of the qHPV vaccine produced robust antibody responses in MAW. At Month 7, 98.4%, 98.1%, 98.8%, and 97.3% of subjects who received qHPV vaccine within the PPI population were anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 seropositive, respectively. As expected, there was an inverse correlation between age at first vaccination and Month 7 anti-HPV levels (see [Appendix 2.5: 14], [Appendix 2.5: 15], [Appendix 2.5: 16], and [Appendix 2.5: 17] of GMTs). However, compared with 16- to 23-year-olds (in the combined immunogenicity database of qHPV vaccine in YAW), the reductions in Month 7 GMTs among 24- to 34-year-olds and 35- to 45-year-olds (in P019) were modest.

Anti-HPV GMTs at Months 24 and 48

At Month 24, 89.3%, 92.4% and 96.5% of subjects who received qHPV vaccine in the PPI population were anti-HPV 6, anti-HPV 11, and anti-HPV 16 seropositive. Only 54.6% of subjects were anti-HPV 18 seropositive at Month 24.

[Appendix 2.5: 18] shows at Month 48, 85.6%, 92.0% and 97.4% were seropositive for HPV 6, HPV 11 and HPV 16. For HPV 18, this proportion was 47.9%. Despite the nominal loss of seropositivity, no cases of HPV 18 infection or disease were observed in subjects who received qHPV vaccine in the primary efficacy population. This observation of protection against HPV type 18 infection or disease has been consistently seen in the Phase II/III development program of the qHPV vaccine. In the HNRT, there was a single case of persistent infection which started between Day 1 and Month 7.

Anti-HPV GMTs in Cord Blood

Maternal-infant transfer of neutralizing anti-HPV was demonstrated in this study at a median of 28 months (range 14 to 43 months) post dose 3 and showed very high correlation coefficients for all HPV types.

Summary – Impact of Age at Vaccination on Anti-HPV Responses. Month 7 anti-HPV responses declined with age at first vaccination. The age-of-vaccination impact on anti-HPV 16 responses was smaller than the impact of age of vaccination on anti-HPV 6, anti-HPV 11, and anti-HPV 18 responses. Despite the lower levels in anti-HPV GMTs at Month 7 and Month 48 related to age at vaccination, vaccine efficacy remained comparable across the 16- to 45-year-old age range.

Merck Sharp & Dohme (Argentina) Inc.
José Abrate
Apoderado

MERCK SHARP & DOHME ARG. INC
Farm. Sebastián Darío Goldentul
DIRECTOR TECNICO
MATRICULA NACIONAL 15436

2.5.4.2.2 Persistence of Anti-HPV Responses

The analyses in this section summarize persistence of immune responses through up to 4 years post-vaccination onset. Among subjects who received qHPV vaccine in the PPI population, the type-specific anti-HPV GMTs reached their highest measured levels at Month 7 and then plateaued from approximately Month 12 until Month 48. At end-of-study, anti-HPV 6, 11, 16, and 18 GMTs were at or above the anti-HPV GMTs observed following natural infection.

2.5.4.2.3 Conclusions Regarding the Immunogenicity of qHPV vaccine

Prophylactic administration of a 3-dose regimen of qHPV vaccine to 24- to 45-year-old women who are naïve to the relevant HPV type(s) at enrollment and remain PCR-negative to the same HPV types(s) through the completion of the vaccination regimen generates robust and durable anti-HPV 6, anti-HPV 11, anti-HPV 16 and anti-HPV 18 responses that result in a high level of protective efficacy through approximately 3.5 years following completion of the vaccination regimen.

2.5.5 Overview of Safety

The Safety Population is defined as all subjects who were enrolled in P019 and who received at least one vaccination. This population included 3819 subjects (1908 subjects who received qHPV vaccine and 1902 subjects who received placebo).

The endpoint-driven CSR reported a general tolerability of qHPV in subjects 24- to 45-years of age. The proportion of subjects who reported an injection-site adverse experience was higher among subjects who received qHPV vaccine compared with placebo subjects, most adverse experiences were judged by the study subjects to be mild or moderate in intensity, and the most common injection-site adverse experiences reported were pain, swelling, and erythema.

The proportions of subjects who reported a systemic clinical adverse experience were comparable between the 2 vaccination groups and the most common reported systemic clinical adverse experiences determined by the investigator to be vaccine related were headache, pyrexia, and nausea.

Data suggest that qHPV vaccine is associated with a modest increase in the incidence of transient low-grade fevers, compared with placebo.

2.5.5.1 Analysis of Adverse Experiences in Safety Population (24- to 45-Year-Old Subjects)

Deaths were rare (7 subjects [0.4%] who received qHPV vaccine and 1 subject [0.1%] who received placebo) [Table 2.7.4: 6].

A total of 24 (1.2%) subjects who received qHPV vaccine and 15 (0.8%) subjects who received placebo experienced a SAE at any time during the study.

The vaccination groups were also comparable with respect to the types of serious adverse experiences reported. The most common serious adverse experiences in both vaccination

Merck Sharp & Dohme (Argentina) Inc.
Apoderado

MERCK SHARP & DOHME ARG. INC
Farm. Sebastián Darío Goldentul
DIRECTOR TECNICO
MATRICULA NACIONAL 15436

groups were infections and pregnancy complications. [Table 2.7.4: 5] lists subjects in the Safety Population with serious clinical adverse experiences.

Overall, 9 subjects discontinued from the study due to an adverse experience. Of these subjects 7 (0.4%) received qHPV vaccine and 2 (0.1%) received placebo.

[Table 2.7.4: 4] summarizes clinical adverse experiences in the Safety Population. Compared with the endpoint-driven CSR, the following new information is noted:

- Three (3) new fatal serious adverse experiences (SAEs) were reported.
- One (1) new injection-site adverse experience was reported.
- Two (2) new systemic adverse experiences were reported.
- Four (4) new serious adverse experiences were reported.
- Two (2) new serious adverse experiences were determined by the investigator to be vaccine-related (these were actually procedure-related SAEs).
- No discontinuations due to an adverse experience were reported.

2.5.5.2 New Medical History in the Safety Population

Medical History at Day 1 was recorded for all subjects. Any acute or chronic medical conditions that occurred during the year prior to study entry were recorded. Any gynecological conditions or procedures that occurred in the subject's lifetime were also recorded. After Day 1, any medical history or gynecological conditions or procedures that occurred since the last study visit were recorded. New medical conditions were not considered adverse experiences when they occurred outside the safety follow-up period (Day 1 through Month 7) and/or were not considered by the study investigators to be vaccine/placebo related.

[Table 2.7.4: 19] presents a cumulative summary of the number and percentage of subjects in the Safety Population with new medical conditions (incidence ≥1% in one or more vaccination groups) by system organ class and vaccination group during the follow-up period (Post Month 7) in the safety population. Of 3681 subjects with follow-up past Month 7, 1943 subjects have reported one or more new medical conditions (958 recipients of qHPV vaccine (51.7%) and 985 recipients of placebo (53.4%). The proportion of subjects reporting new medical conditions was comparable between vaccination groups. The most commonly reported new medical conditions during the follow-up period were bacterial vaginosis (4.5%), nasopharyngitis (3.7%), and upper respiratory tract infection (3.6%).

[Table 2.7.4: 20] presents a summary of new medical conditions potentially consistent with autoimmune phenomena reported post-month 7 among all subjects by vaccination group. The proportions of subjects reporting such events were comparable between the vaccination groups (3.4% and 3.7% in the group that received qHPV vaccine or placebo, respectively). Since the interim report, 3 cases of arthritis were observed, 2 in the qHPV group and 1 in the placebo group.

Merck Sharp & Dohme (Argentina) Inc.
Apoderado

MERCK SHARP & DOHME ARG. INC.
Farm. Sebastián Darío Goldentul
DIRECTOR TECNICO
MATRICULA NACIONAL 15436

2.5.5.3 Safety in Special Groups and Situations

2.5.5.3.1 Intrinsic Factors

Administration of qHPV vaccine (1) is generally well tolerated among 9- to 45-year-old subjects; (2) results in generally comparable safety profiles in 9- to 17-year-old girls, 18- to 26-year-old women, and 27- to 45-year-old women; (3) is generally well tolerated in 9- to 45-year-old subjects who are seropositive to at least one vaccine HPV type at the start of vaccination; and (4) is generally well tolerated in 18- to 45-year-old women who are infected with a vaccine HPV type at the start of vaccination.

The adverse experience profile of qHPV vaccine is not affected by racial background, ethnicity, or continent of origin.

2.5.5.3.2 Extrinsic Factors

Administration of qHPV vaccine is generally well tolerated among subjects, (1) who take immunosuppressive medication within 15 days of any vaccination; (2) who take medications with anti-inflammatory or antipyretic properties within 15 days of any vaccination; and (3) who use hormonal contraceptives at any time during the vaccination period.

2.5.5.3.3 Outcome of Pregnancies

Overall Pregnancy Rates A total of 499 subjects (13.1% of the study population) reported 574 pregnancies (194 pregnancies have been reported since the interim report, 97 in the qHPV group and 97 in the placebo group). A slightly smaller proportion of subjects in the qHPV vaccine group became pregnant compared with the placebo group (12.4% vs. 13.8% respectively). Thus, it can be concluded that administration of qHPV vaccine does not impact the fertility of 24- to 45-year-old women.

Pregnancy Outcomes The proportions of pregnancies resulting in live birth and fetal loss were comparable in the group that received qHPV vaccine compared with the placebo group (78.9% versus 76.9%, and 18.8% versus 21.4% for subjects receiving qHPV vaccine and placebo, respectively).

A common means to evaluate pregnancy outcomes is to calculate the proportions of pregnancies with natural outcomes that ended in a negative outcome as follows:

$$\frac{\text{Number of pregnancy resulting in spontaneous abortion, late fetal death, and congenital anomaly}}{\text{Number of pregnancies (excluding elective abortion and unknown outcomes)}}$$

The proportions of pregnancies with natural outcomes that ended in a negative outcome were 19.1% (49/257) in the group that received qHPV vaccine and 20.3% (56/276) in the placebo group.

Fetal Loss The proportions of pregnancies resulting in fetal loss were comparable between the 2 vaccination groups.

Merck Sharp & Dohme (Argentina) Inc.

MERCK SHARP & DOHME ARG. INC.
Farm. Sebastian Dario Goldenti
DIRECTOR TECNICO
MATRICULA NACIONAL 15436

Live Birth The proportions of pregnancies resulting in a live birth were comparable between the 2 vaccination groups:

- **Congenital Anomalies** [Table 2.7.4: 12] presents an accounting of congenital anomalies by time of detection. There were a total of 14 cases of congenital anomaly, including 8 cases in the group that received qHPV vaccine and 6 cases in the placebo group.
- **Other Medical Conditions** These events included medical conditions consistent with serious adverse experiences that occurred among infants born to study subjects. Such events were comparable among subjects who received qHPV vaccine and subjects who received placebo. The most common 'other medical conditions' were prematurity (4 and 3 infants born to subjects who received qHPV vaccine or placebo, respectively) and respiratory distress (4 and 2 infants born to subjects who received qHPV vaccine or placebo, respectively).

Overall, pregnancy outcomes were comparable among subjects who received qHPV vaccine and subjects who received placebo.

2.5.5.3.4 Administration of qHPV vaccine to Lactating Women

Administration of qHPV vaccine or placebo to nursing mothers was reported and followed for outcome and reported in the endpoint-driven analysis. There were no patterns or trends in the types of serious adverse experiences reported in infants who were breastfed during the vaccination phase of clinical studies. No safety signals of clinical concern were identified among these infants.

2.5.5.4 Postmarketing Safety Data

The post-marketing experience with quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine, MSD, is summarized from the International Birthdate (1-Jun-2006) through 31-May-2009. This vaccine was first licensed on 01-Jun-2006 in Mexico. More than 51,000,000 doses of this vaccine were distributed as of 31-May-2009. The post licensure experiences with the vaccine collected through passive reporting of spontaneous adverse experiences to MSD has confirmed the favorable safety profile of the vaccine.

To permit safety surveillance for its products, MSD maintains the New Worldwide Adverse Experience System (NWAES) database. Postmarketing safety surveillance is a worldwide, passive, spontaneous, and voluntary reporting system. The NWAES database contains all spontaneous adverse experience (AE) reports from the marketed environment, serious reports from clinical trials, and reports from the medical literature. This is a dynamic database, and adverse experience information is updated continuously. The retrieval of data is provided as a snapshot in time.

All of the reports are entered into NWAES and are coded using the terminology of the reporter. The Medical Dictionary for Regulatory Activities (MedDRA) is the dictionary used to code AE terms in the NWAES database. Inclusion of the report in the database

implies only a temporal association, not necessarily a causal association. Each report represents 1 individual who may experience 1 or more AEs. Since each AE is coded to a body system, one report may contain multiple AEs in the same or different body systems.

Routine Pharmacovigilance practices include continuous monitoring of the safety profile of approved products. Data from the NWAES database are routinely reviewed as individual reports and in aggregate. The purpose of the review is to evaluate adverse experience reports for possible safety signals, to determine if further investigation is warranted to clarify the safety profile of the product, and to ensure completeness of safety information in worldwide package circulars.

In August, 2009, the FDA and CDC in the United States issued a statement on the safety of the qHPV vaccine that based on the review of available information, the qHPV vaccine continues to be safe and effective and that its benefits continue to outweigh its risks [Ref. 5.4: 3242]. A summary of data from the U.S. VAERS (Vaccine Adverse Event Reporting System) was also published in the same month, covering the 2.5 years following initial U.S. licensure of the qHPV vaccine in females [Ref. 5.4: 3243]. The conclusion from this review was that the post-licensure safety profile of the qHPV vaccine was broadly consistent with safety data from pre-licensure trials. Overall, the post-marketing safety experience with quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine, MSD, has confirmed the favorable safety profile of the vaccine. There is a low frequency of reported serious adverse events, and the benefit-risk ratio for the product remains favorable. MSD will continue to the monitor the safety of the vaccine in the post-licensure period.

2.5.5.5 Overdose

For HPV vaccine and placebo, overdose was defined as a subject receiving >3 doses (0.5 mL per dose) of vaccine or placebo throughout the study or receiving ≥0.75 mL of vaccine or placebo in any one dose. There were no reports of overdose with qHPV within P019.

2.5.5.6 Drug Abuse/Withdrawal and Rebound/Impairment of Mental Ability

No abuse of qHPV vaccine was reported; qHPV vaccine does not have properties associated with medications with abuse potential. No occurrence of withdrawal or rebound was reported.

The qHPV vaccine does not have biologic properties or physiologic effects that could interfere with the ability to drive or operate machinery or impair mental abilities. Thus, qHPV vaccine does not appear to have any adverse effects on the ability to drive or operate machinery.

Also, qHPV vaccine does not appear to impair mental abilities.

2.5.5.7 Conclusions Regarding the Safety of qHPV vaccine

The safety data in P019 support the conclusion that qHPV vaccine is generally well tolerated and displays a safety profile similar to that shown in prior submissions. Specifically, (1) administration of qHPV vaccine is generally well tolerated in 24- to 45-