

GARDASIL® Update:
Efficacy in Adult Women (24-45 Year-Olds)
End-of-Study Analyses

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A Brief History of P019

2007

- Endpoint-driven tests of efficacy hypotheses
- Mean follow up time of 2.2 years¹
- Data submitted to regulatory authorities

2009

- Epidemiology/natural history data²
- End-of-study efficacy data
- Mean follow up time of 3.8 years
- Update submitted to regulatory authorities

Protocol 019

Study Design

- Randomized, placebo-controlled, double-blind
- International, multi-center
- Fixed event design with 48 month duration
- 3,800 healthy women enrolled from 24 to 45 years of age at time of first vaccination
- 1:1 stratification by age: 24 to 34 years of age and 35 to 45 years of age
- Randomized (1:1) to receive either 3 IM injections of qHPV vaccine or placebo at Day 1, Month 2, and Month 6

Protocol 019

Key Exclusion Criteria

- History of Loop Electrosurgical Excision Procedure (LEEP) or hysterectomy
- History of biopsy-diagnosed cervical HPV disease in past 5 years
- Prior history of genital warts, VIN, or VaIN
- No limitations of lifetime sexual partner number

Protocol 019

Efficacy Demonstration Endpoints

- Primary analysis: per-protocol efficacy population*
- **Co-Primary endpoints**
 - First co-primary: Combined incidence of HPV 6/11/16/18-related persistent infection, CIN, AIS, cervical cancer and EGLs
 - Second co-primary: Combined incidence of HPV 16/18-related persistent infection, CIN, AIS, and cervical cancer and EGLs
- **Secondary endpoint**
 - Combined incidence of HPV 6/11-related persistent infection, CIN, AIS, and cervical cancer and EGLs
- **Tertiary endpoint**
 - Reduction in HPV 6/11/16/18-related abnormal Paps

* HPV DNA negative and seronegative at baseline and HPV DNA negative at month 7 for the relevant HPV type.
Case counting after month 7.

EGLs = external genital lesions (genital warts, VIN, VaIN, vulvar cancer, vaginal cancer)

Natural History Data

Prevalence of Exposure to Multiple Vaccine HPV Types at Day 1

HPV 6, 11, 16 and/or 18	All subjects aged 24-45 (n = 3,819)			
	DNA Only		DNA or Serology	
	m	%	m	%
At least 1 type detected	298	7.8	1,252	32.8
Only 1 type detected	270	7.2	890	23.9
At least 2 types detected	28	0.7	362	9.5
Only 2 types detected	25	0.7	266	7.0
Only 3 types detected	3	0.1	82	2.1
All 4 types detected	0	0.0	14	0.4

m = number of subjects in indicated category.

Conclusion

- 67% of study subjects were negative by both HPV DNA and serology to all 4 vaccine HPV types at baseline
- 90% of study subjects would potentially benefit from protection against 3 or 4 vaccine HPV types

Association of Baseline HPV DNA Detection With Selected Subject Characteristics

Cross-Sectional Analysis

Baseline Characteristics	All 4 types negative (N=3386)	HPV Positive (Prevalent Infection) 6,11,16 &/or 18 (N=291)	Age-adjusted OR (95% CI) for HPV DNA infection at baseline Types 6,11,16 &/or 18
Lifetime # of sexual partners			
1	1369 (95)	48 (3)	1.0
2-3	1066 (91)	93 (8)	2.4 (1.7, 3.4)
≥4	946 (85)	149 (13)	4.1 (2.9, 5.7)
# New sexual partners (last 6 months)			
0	3127 (92)	215 (6)	1.0
1	216 (76)	63 (22)	3.7 (2.7, 5.0)
2-3	28 (65)	13 (30)	5.9 (3.0, 11.7)
≥4	5 (100)	0 (0)	0.0 (0.0, 1)
Marital Status			
Married, first marriage	1451 (96)	57 (4)	1.0
Single, never married	536 (81)	106 (16)	3.9 (2.8, 5.6)
Remarried	197 (92)	14 (7)	1.9 (1.0, 3.4)
Divorced, separated or widowed	263 (86)	36 (12)	3.9 (2.5, 6.1)
Living with partner	939 (91)	78 (8)	1.9 (1.3, 2.7)

Impact Of Selected Baseline Characteristics On The Risk For Incident Infections

Placebo Analysis

Baseline Characteristic	Number	Incident Infection HPV 6,11,16 &/or 18 (n, %) (N=147)	Age-adjusted HR for incident infection (95% CI)
Lifetime # of sexual partners			
1	683	38 (5)	1.0
2-3	517	46 (8)	1.5 (1.0, 2.3)
≥4	476	63 (12)	1.9 (1.3, 2.9)
# New sexual partners (last 6 months)			
0	1539	121 (7)	1.0
1	122	19 (14)	1.5 (0.9, 2.4)
2-3	13	7 (35)	5.2 (2.4, 11.1)
≥4	1	0 (0)	0.0 (0.0, 1)
Marital status			
Married, first marriage	727	33 (4)	1.0
Single, never married	265	51 (16)	2.8 (1.8, 4.4)
Remarried	106	6 (5)	1.3 (0.6, 3.2)
Divorced/separated/widowed	121	18 (13)	3.8 (2.2, 6.8)
Living with partner	461	39 (8)	1.5 (0.9, 2.4)

Summary of Natural History

- **Most women who had evidence of past or current vaccine HPV type infection were infected with only one type**
 - Few women had evidence of past or current infection with 3 or 4 vaccine HPV types
- **Subject characteristics that predicted baseline vaccine HPV type infection were the same characteristics that predicted incident infections**
 - Therefore making the identification of a risk demographic difficult to identify

Efficacy

Vaccine Type Analyses
(Endpoints Related to HPV 6/11/16/18)

Primary Efficacy Results

HPV 6/11/16/18-Related Persistent Infection, CIN, or EGL *Co-Primary Endpoint*

Per Protocol Efficacy Population

Endpoints	Gardasil (N=1910)	Placebo (N=1907)	Observed Efficacy (%)	95% CI
	# of Cases	# of Cases		
HPV 6/11/16/18-Related Persistent Infection, CIN, or EGL	10	86	88.7	78, 95

Primary Efficacy Results

HPV 6/11/16/18-Related Persistent Infection, CIN, or EGL

Co-Primary Endpoint by Age Strata

Per Protocol Efficacy Population

Endpoints	Gardasil (N=1910)	Placebo (N=1907)	Observed Efficacy (%)	95% CI
	# of Cases	# of Cases		
HPV 6/11/16/18-Related Persistent Infection, CIN, or EGL	10	86	88.7	78, 95
24 to 34 year-olds	5	56	91.3	78, 97
35 to 45 year-olds	5	30	83.8	58, 95

Primary Efficacy Results

HPV 6/11/16/18-Related Persistent Infection, CIN, or EGL Co-Primary Endpoint by Disease Severity

Per Protocol Efficacy Population

Endpoints	Gardasil (N=1910)	Placebo (N=1907)	Observed Efficacy	95% CI
	# of Cases	# of Cases	(%)	
Persistent Infection, CIN, or EGL	10	86	88.7	78, 95
Persistent Infection	9	85	89.6	79, 95
CIN (any grade)	1	17	94.1	63, 100
CIN 2/3 or worse	1	6	83.3	-38, 100
EGL	0	7	100	31, 100
Condyloma	0	7	100	31, 100
VIN 2/3 or VaIN 2/3	0	0	NA	NA

Primary Efficacy Results

HPV 6/11/16/18-Related Persistent Infection, CIN, or EGL

Co-Primary Endpoint by HPV Type

Per Protocol Efficacy Population

Endpoints	Gardasil (N=1910)	Placebo (N=1907)	Observed Efficacy (%)	95% CI
	# of Cases	# of Cases		
Persistent Infection, CIN, or EGL	10	86	88.7	78, 95
HPV 6	2	35	94.4	78, 99
HPV 11	0	4	100	-52, 100
HPV 16	8	39	79.9	56, 92
HPV 18	0	13	100	67, 100

HPV 6/11/16/18-Related Persistent Infection, CIN, or EGL

Full Analysis Set Population

Endpoints	Gardasil (N=1910)	Placebo (N=1907)	Observed Efficacy	95% CI
	# of Cases	# of Cases	(%)	
Persistent Infection, CIN, or EGL	116	214	47.2	34, 58

HPV 6/11/16/18-Related Persistent Infection, CIN, or EGL By Disease Severity

Full Analysis Set Population

Endpoints	Gardasil (N=1910)	Placebo (N=1907)	Observed Efficacy (%)	95% CI
	# of Cases	# of Cases		
Persistent Infection, CIN, or EGL	116	214	47.2	34, 58
Persistent Infection	110	211	49.0	36, 60
CIN (any grade)	29	55	47.5	16, 68
CIN 2/3 or worse	21	27	22.4	-43, 58
EGL	11	12	8.5	-127, 63
Condyloma	7	12	41.8	-60, 81
VIN 2/3 or VaIN 2/3	2	0	NA	NA

Primary Efficacy Results

HPV 6/11/16/18-Related Persistent Infection, CIN, or EGL Co-Primary & Secondary Endpoints

Per Protocol Efficacy Population

Endpoints	Gardasil (N=1910)	Placebo (N=1907)	Observed Efficacy (%)	95% CI
	# of Cases	# of Cases		
HPV 16/18-Related Persistent Infection, CIN, or EGL	8	51	84.7	68, 94
HPV 6/11-Related Persistent Infection, CIN, or EGL	2	38	94.8	80, 99

Primary Efficacy Results

HPV 6/11/16/18-Related Persistent Infection, CIN, or EGL Co-Primary & Secondary Endpoints by Age Strata

Per Protocol Efficacy Population

Endpoints	Gardasil (N=1910)	Placebo (N=1907)	Observed Efficacy (%)	95% CI
	# of Cases	# of Cases		
HPV 16/18-Related Persistent Infection, CIN, or EGL	8	51	84.7	68, 94
24 to 34 year-olds	5	35	86.0	64, 96
35 to 45 year-olds	3	16	81.8	36, 97
HPV 6/11-Related Persistent Infection, CIN, or EGL	2	38	94.8	80, 99
24 to 34 year-olds	0	24	100	83, 100
35 to 45 year-olds	2	14	86.2	40, 99

Impact of GARDASIL on Incidence of HPV 6/11/16/18-related Pap Diagnoses (ASC-US or worse)

Tertiary Endpoint

Per Protocol Efficacy Population

Endpoints	Gardasil (N=1910)	Placebo (N=1907)	Observed Efficacy (%)	95% CI
	# of Cases	# of Cases		
HPV 6/11/16/18-Related ASC-US HR-HPV positive, or worse	1	38	97.4	85, 100

Impact of GARDASIL on Incidence of HPV 6/11/16/18-related Pap Diagnoses (ASC-US or worse)

Tertiary Endpoint by Age Strata

Per Protocol Efficacy Population

Endpoints	Gardasil (N=1910)	Placebo (N=1907)	Observed Efficacy (%)	95% CI
HPV 6/11/16/18-Related ASC-US HR-HPV positive, or worse	1	38	97.4	85, 100
24 to 34 year-olds	1	25	95.9	75, 100
35 to 45 year-olds	0	13	100	68, 100

Impact of GARDASIL on Incidence of HPV 6/11/16/18-related Pap Diagnoses (ASC-US or worse)

Full Analysis Set

Endpoint	GARDASIL™ (N=1910)	Placebo (N=1907)	Observed Efficacy (%)	95% CI
HPV 6/11/16/18-Related ASC- US HR-HPV positive, or worse	35	70	50.1	24, 68
24-34 year-olds	23	50	52.6	21, 72
35-45 year-olds	12	20	42.0	-25, 74

Impact of GARDASIL on Incidence of Pap Test Abnormalities Due to Any HPV Type (ASC-US or worse)

Full Analysis Set

Endpoint	GARDASIL™ (N=1910)	Placebo (N=1907)	Observed Efficacy (%)	95% CI
ASC- US HR-HPV positive, or worse	258	271	5.0	-13, 20
By Severity				
ASC-US HR-HPV positive	133	120	-10.9	-43, 14
LSIL	182	183	0.5	-23, 19
ASC-H	11	12	8.5	-127, 63
HSIL	11	11	0.1	-154, 61
AGC	3	4	25.1	-343, 89

Clinical Adverse Experience Summary

	Gardasil (N=1890)		Placebo (N=1888)	
	n	%	n	%
Number (%) of subjects:				
With 1 or more AEs	1645	87.0	1535	81.3
With injection-site AEs	1450	76.7	1213	64.2
With systemic AEs	1121	59.3	1135	60.1
With serious AEs	14	0.7	16	0.8
With serious vaccine-related AEs*	0	0.0	0	0.0
Who died†	7	0.4	1	0.1
Discontinued due to an AE	7	0.4	2	0.1
Discontinued due to a serious AE	2	0.1	0	0.0
Discontinued due to a serious vaccine-related AE	0	0.0	0	0.0

*Determined by the investigator to be possibly, probably, or definitely related to the vaccine.

†All deaths in the study were determined by the investigator to be "definitely not" related to the vaccine. Vaccine: hypertensive heart disease, nasopharyngeal cancer, breast cancer, pulmonary tuberculosis, cardiac failure from hyperthyroidism, post-operative PE, pericarditis secondary to SLE. Placebo: Acute lymphoblastic Leukemia

N = number of subjects with follow-up

Summary and Conclusions

- Women aged 24 to 45 are susceptible to HPV 6/11/16/18 infection and disease
- Women aged 24 to 45 are at continued risk for acquiring infection and disease lesions from these HPV types
- Gardasil is highly efficacious against HPV 6/11/16/18-related persistent infection, CIN or EGL in adult women negative to the relevant HPV type
 - Efficacy supported by significant efficacy for the primary endpoint in the intention-to-treat population analyses
- GARDASIL is generally safe and well tolerated in women aged 24 to 45 years old