GARDASIL® Update:
End-of-Study (16-26 year-olds)
Adult Women (24-45 year-olds)

ACIP
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Richard M. Haupt, MD, MPH
Clinical Research
Infectious Diseases & Vaccines
Merck Research Laboratories

Presentation Outline

- Young Adult Women (16-26 year-olds)
  - End-of-Study vaccine efficacy
    - Prophylactic efficacy
    - Efficacy in previously exposed females
- Adult Women (24-45 year-olds)
  - Study overview/Demographics
  - Vaccine efficacy
  - Vaccine safety
  - Population benefit
    - Susceptibility and Acquisition of Infection
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Prophylactic Efficacy of GARDASIL®
CIN & AIS

Per-Protocol Population (Protocols 007, 013, and 015)
Mean Follow-Up - 44 months

Endpoint**	GARDASIL® Cases (N = 9075)	Placebo Cases (N = 9075)	% Efficacy	95% CI
HPV 6/11/16/18-related CIN or AIS	9	225	96	(92, 98)
By Type				
HPV 6-related	0	47	100	(92, 100)
HPV 11-related	0	12	100	(65, 100)
HPV 16-related	8	137	94	(89, 98)
HPV 18-related	1	61	98	(91, 100)
By Disease				
CIN 1	7	170	96	(91, 98)
CIN 2/3	2*	110	98	(93, 100)
AIS	0	7	100	(31, 100)

** Subjects are counted only once per row, but may be in more than one row
* One case was a co-infection with HPV 52, the other was a co-infection with HPV 51 & 56

Prophylactic Efficacy of GARDASIL®
External Genital Lesions

Per-Protocol Population (Protocols 007, 013, and 015)

Mean Follow-Up - 44 months

Endpoint*	GARDASIL® Cases (N = 9075)	Placebo Cases (N = 9075)	% Efficacy	95% CI
HPV 6/11/16/18-related Ext Gen Lesion	2	227	99	(97, 100)
By Type				
HPV 6-related	2	179	99	(96, 100)
HPV 11-related	0	36	100	(89, 100)
HPV 16-related	0	46	100	(92, 100)
HPV 18-related	0	13	100	(68, 100)
By Disease				
Genital Warts	2	193	99	(96, 100)
VIN 1 or VaIN 1	0	28	100	(86, 100)
VIN 2/3 or VaIN 2/3	0	23	100	(83, 100)

* Subjects are counted only once per row, but may be in more than one row

Efficacy Against HPV 6,11,16, 18-Related Disease by Baseline Serostatus and PCR Status

MITT-2 Analysis (Protocols 007, 013, and 015)*

Endpoint	HPV Vaccine Cases (N = 9075)	Placebo Cases (N = 9075)	% Efficacy	95% CI
Sero Negative & PCR Negative				
CIN (any grade)	16	309	95	(92, 97)
EGL	11	303	96	(94, 98)
Sero Positive & PCR Negative				
CIN (any grade)	0	7	100	(29, 100)
EGL	0	8	100	(40, 100)
Sero Negative & PCR Positive				
CIN (any grade)	83	101	22	(-6, 42)
EGL	46	43	-4	(-62, 33)
Sero Positive & PCR Positive				
CIN (any grade)	105	113	5	(-25, 28)
EGL	14	16	12	(-93, 60)

* MITT-2: Received at least one dose, case counting starts 30 days after dose 1

Summary

- Prophylactic efficacy of GARDASIL® in 16- to 26-year-old women is high through Year 4
  - Point estimates for efficacy against disease endpoints close to 100%
- Efficacy was also seen in the subset of 16-26 year-old women who were PCR Negative and Seropositive at baseline
- No efficacy (positive or negative) was seen in the subset of women PCR Positive and Seropositive at baseline

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Extending the Efficacy in Young Adult Women to Adult Women

- Administration of GARDASIL® is highly effective in preventing HPV 6/11/16/18-related cervical, vulvar and vaginal disease in young women
- Immunogenicity alone is not an appropriate metric for evaluating efficacy in adult women
  - Immune correlate of efficacy has not been defined
  - Immune response to vaccination declines with age
  - Efficacy studies in adult women are feasible
- An efficacy demonstration provides the requisite rigor to extend findings from young adult women to adult women
  - Efficacy against persistent Infection and disease sufficient

Efficacy Study in Adult Women

Protocol 019

- **Multi-Center, International Study**
  - 27% US/EU
  - 42% Latin America
  - 31% Asia
- **24- to 45-Year-Old Women (N=3819)**
  - 1:1 randomization (GARDASIL® or placebo)
  - 1:1 stratification (24-34 year-olds or 35-45 year-olds)
- **Key Exclusion Criteria**
  - No history of LEEP or hysterectomy
  - No history of cervical biopsy in past 5 years
  - No history of genital warts
  - No limitation of lifetime sex partners (LSP)
- **Visit Structure**
  - Follow-up for 48 Months
  - Pap test, cervicovaginal sampling at ~6 month intervals
  - Colposcopy for ≥ASC-US

Efficacy Study in Adult Women
Primary Efficacy Endpoints

Protocol 019

- **Co-Primary endpoints**
  - First co-primary: Combined incidence of persistent infection, CIN, or external genital lesions (EGLs) caused by HPV 6, 11, 16, or 18
  - Second co-primary: Combined incidence of persistent infection, CIN or EGLs caused by HPV 16 or 18
- **Secondary endpoint**
  - Combined incidence of persistent infection, CIN, or EGLs caused by HPV 6 or 11
- **Tertiary endpoint**
  - Combined incidence of HPV 16/18-related abnormal Pap test results (ASC-US HR+, LSIL, HSIL, AGC, cancer)

Adult Women (Protocol 019)
24-45 year-old women
Baseline Characteristics

Parameter	GARDASIL® (N = 1911)	Placebo (N = 1908)
% Non-Virgins	100	100
Median (SD) Age at Sexual Debut (Years)	18 (3.7)	18 (3.7)
Lifetime Number of Sex Partners		
0 to 2	58%	58%
3 to 4	19%	19%
>4	23%	23%

Adult Women (Protocol 019)
24-45 year-old women
HPV 6/11/16/18 Status at Baseline

Day 1 Result	GARDASIL® N = 1911 (%)	Placebo N = 1908 (%)
Negative to all 4 HPV Types (Serology and PCR)	**67**	**68**
Positive to ≥1 HPV Type (Serology and/or PCR)	33	32
Exactly 1 HPV Type	25	22
Exactly 2 HPV Types	6	8
Exactly 3 HPV Types	2	2
Exactly 4 HPV Types	0.4	0.3
Positive to 16 & 18	1.0	1.6
Baseline Serology/PCR Results Unknown	0.3	0.5

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

Per-Protocol Efficacy Population

Mean Follow-Up 2.2 Years

Endpoint	GARDASIL® (N=1910)	Placebo (N=1907)	Efficacy (%)	95% CI	P-value
HPV 6/11/16/18-Related Persistent Infection, CIN or EGL	4*	41	91	(74, 98)	<0.001
24 to 34 year-olds	2	24	92	(67, 99)	
35 to 45 year-olds	2	17	89	(52, 99)	
HPV 16/18-Related Persistent Infection, CIN or EGL	4	23	83	(51, 96)	<0.001
24 to 34 year-olds	2	13	85	(34, 98)	
35 to 45 year-olds	2	10	81	(9, 98)	
HPV 6/11-Related Persistent Infection, CIN or EGL	0	19	100	(79, 100)	<0.001
24 to 34 year-olds	0	12	100	(64, 100)	
35 to 45 year-olds	0	7	100	(34, 100)	

* All cases were due to Type 16; 3 were persistent infection, 1 was a CIN 2 co-infection with Type 52

HPV 6/11/16/18-Related Disease Endpoints

Protocol 019 Per Protocol Efficacy Population
Mean Follow-Up 2.2 Years

Endpoint	GARDASIL®	Placebo	Efficacy (%)	95% CI
HPV 6/11/16/18-Related CIN or EGL	**1**	**13**	**92**	**50, 100**
HPV 16/18-Related CIN or EGL	1	8	88	9, 100
HPV 6/11-Related CIN or EGL	0	6	100	16, 100

HPV 16/18-Related Abnormal Pap Tests

Protocol 019 Per Protocol Efficacy Population

Mean Follow-Up 2.2 Years

HPV 16/18-Related Endpoint	GARDASIL®	Placebo	% Reduction	95% CI
ASC-US(HR+) or Worse	**1**	**17**	**94**	**63, 100**
ASC-US HR(+)	1	7	86	-9, 100
LSIL or Worse	0	11	100	61, 100
LSIL	0	10	100	56, 100
ASC-H	0	1	100	--
HSIL	0	0	--	--

ACS-US (HR+) – Atypical squamous cells – undetermined significance (HPV HR Type +)
LSIL – Low-grade squamous intraepithelial lesion
ASC-H – Atypical squamous cells – can not rule out HSIL
HSIL – High-grade squamous intraepithelial lesion

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Safety Profile
Protocol 019
Prespecified Endpoints

Parameter	GARDASIL®		Placebo		Risk Difference (G-P)	95% CI	P-Value†
	n	%	n	%			
Subjects With Follow-up	1889		1886				
SAEs	3	0.2	7	0.4	-0.2	(-0.6, 0.1)	0.204
VR-SAEs	0	0.0	0	0.0	0.0	(-0.2, 0.2)	1.000
Injection Site AEs	1443	76	1210	64	12	(9, 15)	
Erythema	273	15	200	11	4	(2, 6)	<0.001
Pain	1423	75	1170	62	13	(10, 16)	<0.001
Pruritus	31	2	25	1	0.3	(-0.5, 1)	
Swelling	353	19	214	11	7	(5, 10)	<0.001
Warmth	18	1	14	1	0.2	(-0.4, 0.8)	

† Unadjusted for multiple comparisons

SAE = Serious Adverse Experience
VR-SAEs = Vaccine-related SAEs

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Population Benefit

- Population benefit analyses for Adult Women planned for end-of-study (4 years)
- Use current epidemiology to define the population benefit of vaccinating 24-45 year-old women
- Population benefit is a balance between susceptibility to vaccine HPV types and the likelihood of acquiring new infections/disease from vaccine HPV types
  - Susceptibility
    - Baseline HPV DNA prevalence and HPV seropositivity
  - Acquisition of infection
    - Placebo analysis for incident & persistent infections by age groups

Susceptibility
HPV DNA Prevalence
Literature Review and Merck Protocol 019 Baseline Analysis

- Limited data on vaccine type prevalence
  - Type specific data exists mostly for types 16 & 18
- Most studies demonstrate low prevalence for types 16 & 18

Literature Review - HPV DNA Prevalence

Age	HPV Prevalence (%)	
	16	18
~24-34 year-olds	4-6	1-2
~35-45 year-olds	1-2.5	0.5-1

Baseline data (Protocol 019)

Age	HPV Prevalence (%)			
	6	11	16	18
24-34 year-olds	2.4	0.4	6.1	2.5
35-45 year-olds	1.4	0.1	2.8	1.6

Susceptibility
HPV Seroprevalence

Literature Review and Merck Protocol 019 Baseline Analysis

- May represent a closer approximation of cumulative HPV exposure
  - Still an underestimate – not all infected women develop measurable antibody response

Literature Review – HPV Seroprevalence/Vaccine HPV Types

Age	HPV Seroprevalence (%)	
	16	18
~24-34 year-olds	8-19	4-13.7
~35-45 year-olds	12-23.9	6-18.1

Baseline data (Protocol 019)

Age	HPV Prevalence (%)			
	6	11	16	18
24-34 year-olds	14.4	4.6	14.9	5.7
35-45 year-olds	15.3	5.1	14.5	5.2

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)

Acquisition of Infection

Placebo Arm Analysis

Incidence Rates by Age of HPV Infection (per 100 Person-Years)*

Infection	16-26 year-olds (Protocol 012)	24-34 year-olds (Protocol 019)	35-45 year-olds (Protocol 019)
Incident			
16	--	3.4 (2.6, 4.5)	1.1 (0,7, 1.7)
18	--	0.9 (0.6, 1.5)	0.7 (0.4, 1.2)
Persistent			
16	3.5	1.5 (1.0, 2.3)	0.6 (0.3, 1.1)
18	1.2	0.5 (0.2, 0.9)	0.2 (0.1, 0.6)

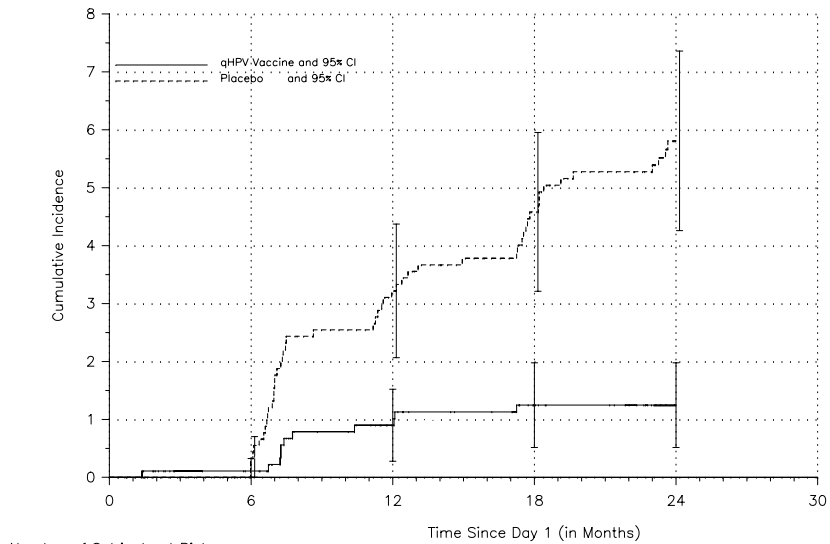
* as measured from cervical and/or external genital swabs among women PCR Negative and SERO Negative at baseline

Incident – Detection of HPV DNA in cervicovaginal specimens at least once post-day 1 in women naïve to the relevant vaccine HPV type at day 1

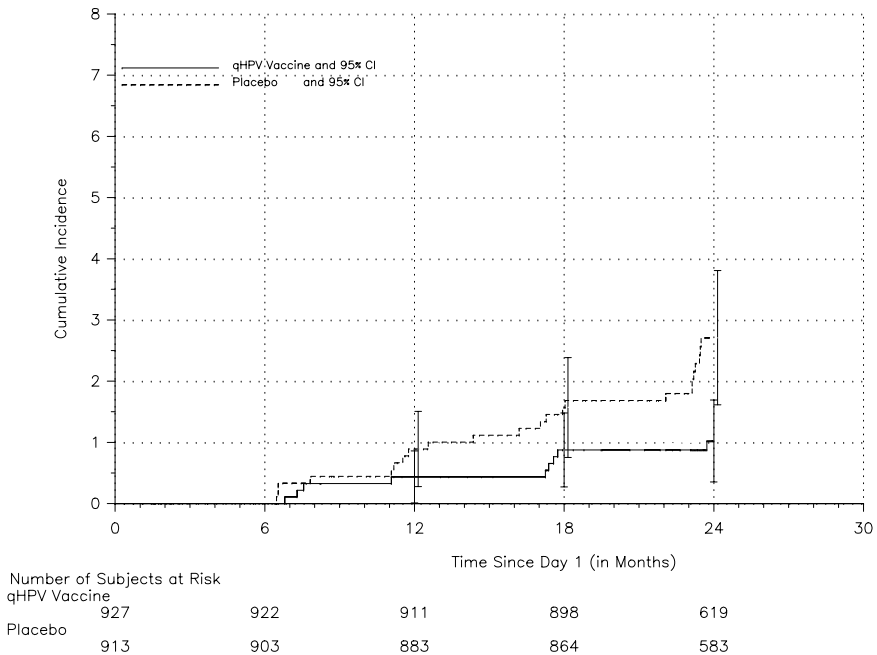
Persistent – Detection of HPV DNA on at least 2 consecutive visits in women naïve to the relevant HPV type at day 1

Analysis of Time to HPV 6/11/16/18-Related Persistent Infection, CIN, and EGL by Age Group

(MITT-2 Population Analysis)



24 to 34 Year-Olds



35 to 45 Year-Olds

* MITT-2: Received at least one dose, case counting starts 30 days after dose 1

Impact of Selected Baseline Characteristics on the Risk for Developing Incident Genital HPV Infection

Placebo Arm Analysis

Baseline Characteristics	No incident infection (N=1680)	Incident HPV Positive Any Vaccine Type (N=147)	Age-adjusted hazard ratio (risk) for incident infection (95%) Types 6,11,16 &/or 18
Lifetime # of sexual partners			
1	683 (95))	38 (5)	1.0
2-3	517 (92)	46 (8)	1.5 (1.0, 2.3)
≥4	476 (88)	63 (12)	1.9 (1.3, 2.9)
# New sexual partners (last 6 months)			
0	1539 (93)	121 (7)	1.0
1	122 (87)	19 (14)	1.5 (0.9, 2.4)
2-3	13 (65)	7 (35)	5.2 (2.4, 11.1)
≥4	1 (100)	0 (0)	0.0 (0.0, 1)
Marital status			
Married, first marriage	727 (96)	33 (4)	1.0
Single, never married	265 (84)	51 (16)	2.8 (1.8, 4.4)
Remarried	106 (95)	6 (5)	1.3 (0.6, 3.2)
Divorced/separated/widowed	121 (87)	18 (13)	3.8 (2.2, 6.8)
Living with partner	461 (92)	39 (8)	1.5 (0.9, 2.4)

Susceptibility & Acquisition of Infection *Summary*

- Majority of 24-45 year-old women remain susceptible to vaccine HPV types
- 24- to 45-year-old women continue to acquire infections with vaccine HPV types
- Incidence for vaccine type infections is inversely related to age
- The subject characteristics that predict baseline HPV prevalence are the same subject characteristics that predict likelihood of acquiring new infections

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- Prophylactic efficacy of GARDASIL® in 16- to 26-year-old women is high through year 4
- Efficacy of GARDASIL® was also seen in the subset of 16-26 year-old women who were PCR Negative and Seropositive to vaccine HPV types at baseline
- High prophylactic efficacy is also seen in 24-45 year-old adult women
- GARDASIL® is generally well tolerated in adult women
- Work to define public health impact in adult women is on-going