

# GARDASIL® Update

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# Presentation Outline

- Licensures & Recommendations
- Updated prophylactic efficacy
- Updated population impact
- Ongoing Studies
- VAERS Update

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# Approved in ~80 Countries / Territories

## North America:

**3**  
Canada  
Mexico  
USA

## Caribbean:

**9**  
Aruba, Barbados,  
Bahamas, Bermuda,  
Cayman Island, Curacao,  
Dominican Republic,  
Trinidad, Puerto Rico

## Central America:

**3**  
Costa Rica, Guatemala,  
Nicaragua

## South America:

**6**  
Argentina, Brazil,  
Chile, Colombia,  
Ecuador, Peru

**35**

Europe (EU): Austria, Belgium, Estonia, Finland, France, Cyprus, Czech Republic, Denmark, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, The Netherlands, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, UK, Bulgaria, Romania

Europe (non-EU): Croatia, Iceland, Norway, Serbia, Turkey, Russia, Switzerland, Bosnia

## Middle East and Africa:

**12**  
Chad, Israel, Central African Republic,  
Congo Kinshasa, Ethiopia,  
Kenya, Mauritius, Morocco,  
Togo, United Arab Emirates,  
Guinea Equatorial,  
Mauritius

## Asia Pacific:

**11**  
Australia, Hong Kong,  
Indonesia, Korea, Macau,  
Malaysia, New Zealand,  
Philippines, Taiwan, Thailand,  
Singapore

# Policy Recommendations



	Females																		Males	Commentary
	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26		
<b>North America</b>																				
USA	A	A	B	B	C	C	C	C	C	C	D	D	D	D	D	D	D	D		B – primary cohort A,C –catch up D – recommended
Canada	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A		A – Recommended funding planned
<b>Europe</b>																				
Austria	A	A	A	A	A	A	A	B	B	B	B	B	B	B	B	B	B	B	A 9-15	A – primary B – catch up
Belgium		A	A	A	A	B	B	C	C	C	C	C	C	C	C	C	C	C		A – primary B – catch up C – select catch up
Cyprus	A	A	A	A	A	A	A	B	B	B	B	B	B	B	B	B	B	B	A 9-15	A – primary B – catch up
France						A	B	B	B	B	B	B	B	B	B					A – primary B – catch up
Germany				A	A	A	A	A	A											A - primary
Italy				A																A – primary; 100% reimb.
Luxemburg			A	A	B	B	B	B	B	B										A – primary B – catch up
Norway			A	A	B	B	B	B												A – primary B – catch up
Serbia																				
Slovakia				A																A – primary; 10% reimb.
Sweden					A	A	A	A	A											A – primary; reimb.
<b>Asia Pacific</b>																				
Australia				A	A	B	B	B	B	B	B	B	B	B	B	B	B	B		A – primary 100% reimb. B – catch up 100% reimb.
<b>Latin America</b>																				
None																				

■ Public Sector Funding
 ■ Private Sector Funding
 ■ Both

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# Clinical Efficacy Program for GARDASIL® in 20,541 Young Women

Study	N	Study Objectives
005	2391	Efficacy through 4 years (HPV 16 vaccine)
007	552	Efficacy through 3 years (GARDASIL®)
	234	Efficacy through 5 years (GARDASIL®) Demonstration of Immune Memory
013	5442	Efficacy and population impact through 4 years (CIN/Warts)
015	12167	Efficacy and population impact through 4 years (CIN 2/3 or AIS)
015NCR	5500	Long-term population effectiveness

# HPV 16/18-Related Cervical, Vulvar, Vaginal Cancer Efficacy (Via Surrogates)

Per-Protocol Efficacy Population - Protocols 007, 013, 015

HPV 16/18-Related	Analysis	GARDASIL®	Placebo	% Efficacy	95% CI
CIN 2/3 or AIS	~ 2 years	0	41	100	91, 100
	~ 3 years	1	73	99	92, 100
VIN 2/3 or VaIN 2/3	~ 2 years	0	10	100	56, 100
	~ 3 years	0	15	100	72, 100

# Case of HPV 16-Related CIN 3 in Subject Who Received GARDASIL®

HPV	Day 1		Month 7		Month 13.5		Month 32.5		Month 33.6				
	Swab	Swab	Swab	Swab	Biopsy	ECC	Biopsy	ECC	Biopsy	LEEP 1	LEEP 2	LEEP 3	LEEP 4
52	+	+	NT	NT	-	-	+	-	+	+	+	+	+
16	-	-	-	-	-	-	+	-	-	-	-	-	-

Path Panel Diagnosis = CIN 3

- This case is likely contamination (cannot rule out true endpoint)
- No cases with similar pattern observed in any placebo subjects in P015)
- Anti-HPV levels not tested (not in consistency lot substudy of P015)

# HPV 6/11/16/18-Related Cervical, Vulvar, and Vaginal Disease

Per-Protocol Efficacy Population - Protocols 007, 013, 015

HPV 6/11/16/18-Related	Analysis	GARDASIL®	Placebo	% Efficacy	95% CI
CIN (any Grade) or AIS	~ 2 years	4	83	95	87, 99
	~ 3 years	6 <sup>†</sup>	148	96	91, 99
Vulvar and Vaginal Lesions (incl. Genital Warts)	~ 2 years	1	113	99	95, 100
	~ 3 years	2 <sup>†</sup>	189	99	96, 100

<sup>†</sup> New cases:

- HPV 16/52 CIN 3 as described previously
- HPV 18/56 CIN 1 (prevalent, persistent HPV 56 infection, HPV 56-related CIN 1; single time detection of HPV 18)
- HPV 6/59 genital wart

# Conclusions – Prophylactic Efficacy

- Prophylactic administration of GARDASIL® is highly effective in reducing the incidence of:
  - HPV 16/18-related cervical, vulvar, and vaginal cancer
  - HPV 6/11/16/18-related CIN (or AIS)
  - HPV 6/11/16/18-related external genital lesions
- Previously presented data
  - High efficacy maintained through Year 5
  - Long-lived immune memory

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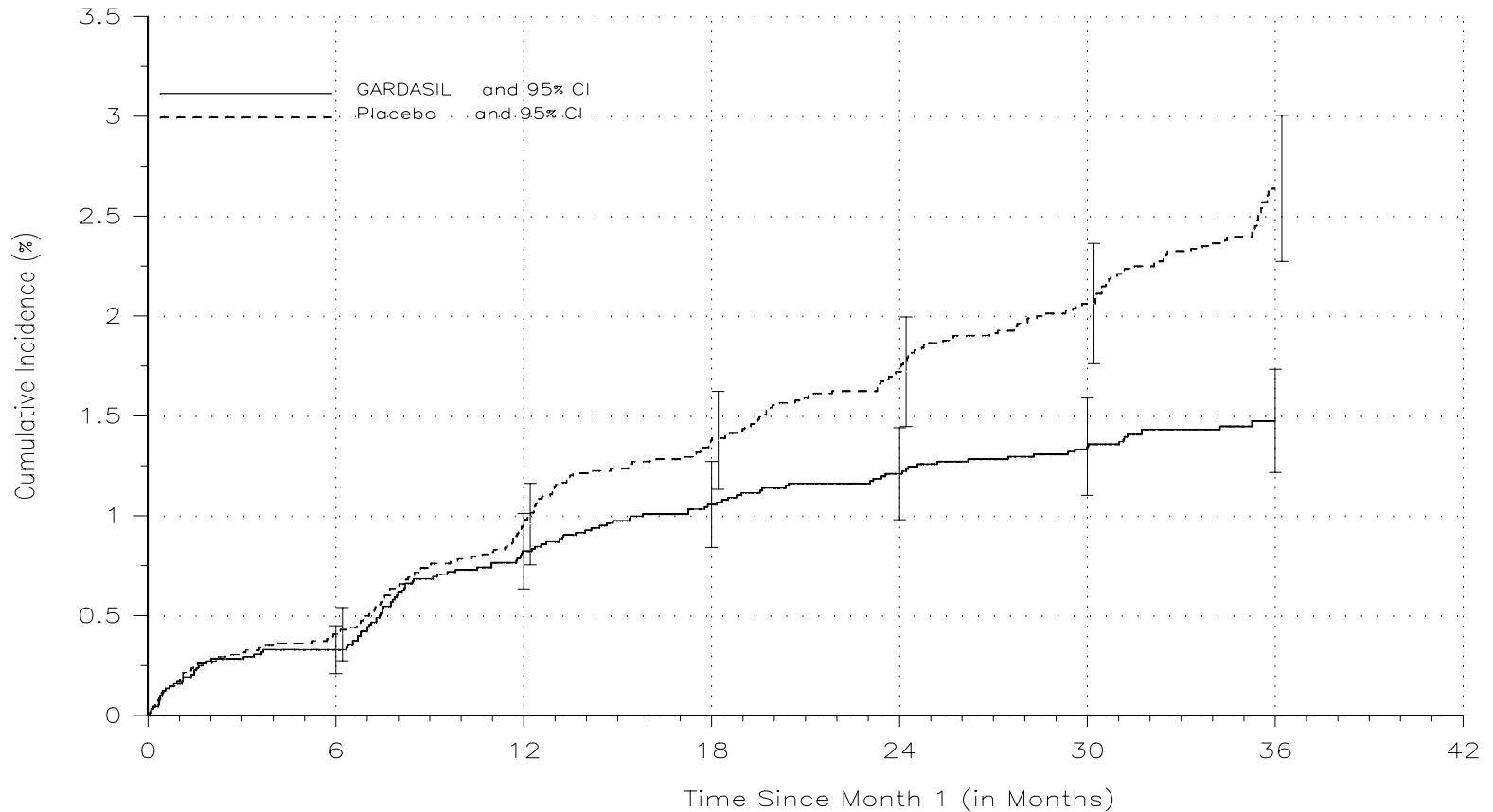
# HPV 16/18-Related Cervical, Vulvar, Vaginal Cancer Efficacy (Via Surrogates)

All Subjects, Including HPV-infected Women -Prot 007, 013, 015

HPV 16/18-Related	Analysis	GARDASIL®	Placebo	% Efficacy	95% CI
CIN 2/3 or AIS	~ 2 years	117	178	34	16, 48
	~ 3 years	137	232	41	27, 53
VIN 2/3 or VaIN 2/3	~ 2 years	8	26	69	30, 88
	~ 3 years	9	31	71	37, 88

# Time to HPV 16/18-Related CIN 2/3 or AIS

All Subjects, Including HPV-infected Women -Prot 007, 013, 015



Number of Subjects at Risk

GARDASIL	8,817	8,728	8,537	8,419	8,154	7,934	2,544
Placebo	8,847	8,750	8,545	8,398	8,139	7,887	2,575

Graphs truncated at M36 (few subjects with follow-up at M42)

# HPV 6/11/16/18-Related Cervical, Vulvar, and Vaginal Disease

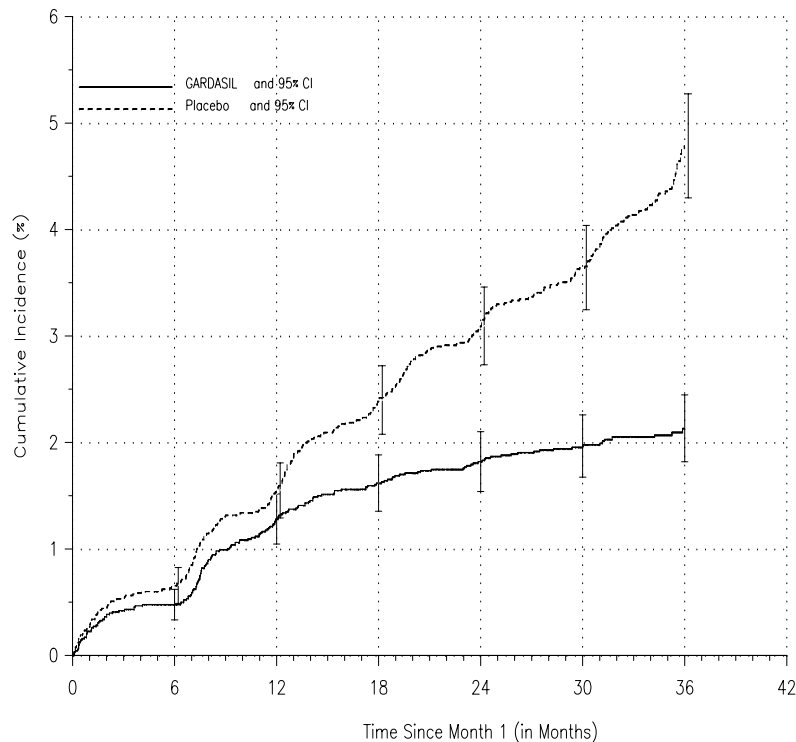
All Subjects, Including HPV-infected Women -Prot 007, 013, 015

HPV 6/11/16/18-Related	Analysis	GARDASIL®	Placebo	% Efficacy	95% CI
CIN (any Grade) or AIS	~ 2 years	170	317	46	35, 56
	~ 3 years	192	414	54	45, 61
Vulvar and Vaginal Lesions (incl. Genital Warts)	~ 2 years	68	229	70	61, 78
	~ 3 years	72	319	78	71, 83

# Time to HPV 6/11/16/18-Related Cervical, Vulvar, and Vaginal Disease

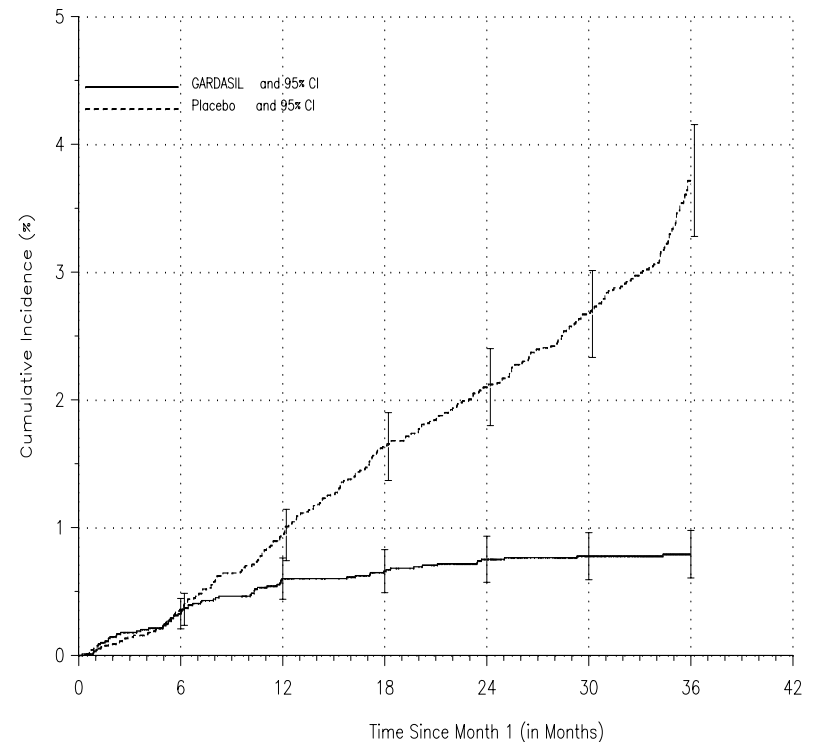
All Subjects, Including HPV-infected Women -Prot 007, 013, 015

## CIN (any grade) or AIS



	0	6	12	18	24	30	36
Number of Subjects at Risk							
GARDASIL	8,817	8,718	8,507	8,386	8,126	7,908	2,535
Placebo	8,847	8,736	8,506	8,330	8,048	7,794	2,518

## External Genital Lesions



	0	6	12	18	24	30	36
Number of Subjects at Risk							
GARDASIL	8,954	8,767	8,621	8,561	8,378	8,225	2,447
Placebo	8,964	8,792	8,612	8,496	8,291	8,082	2,417

Graphs truncated at M36 (few subjects with follow-up at M42)

# Impact of GARDASIL® on Non-Vaccine HPV Types (“Cross-Protection”)

- Protocol 013/015 combined clinical disease analysis
  - Cervical, vulvar, and vaginal disease impact
- Protocol 013 substudy – persistent infection efficacy
- Cross-protection against disease endpoints (CIN 2/3) seen for multiple types that account for an additional 10-15% of the global burden of cervical cancer
- Public presentations in 2007

# Conclusions

## Population Impact

- In girls and women, administration of GARDASIL® reduces overall risk of
  - cervical, vulvar, and vaginal cancer
  - CIN
  - genital warts
- Reductions in Pap test abnormalities, cervical procedures observed
- Benefits becomes more apparent over time
- Cross-protection efficacy in evaluation

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# Ongoing Studies

Study	Title	N	Objectives	FPE	LPO
013/015	Ph III Efficacy	17936	Cervical/Vulvar/Vaginal Cancer and Genital Warts Efficacy Program	2001	2007
015-20	LTFU Study	5496	Duration of efficacy of GARDASIL™ Long-term safety/immunogenicity	2003	2017
018-10	Ig/Effectiveness	1450	Adolescent Long-term Effectiveness, Immunogenicity, and Safety	2003	2016
019	Mid-Adult Women	3819	Bridge indications from young women to mid-adult women	2004	2009
020	Young Men	4079	Efficacy against genital warts, persistent infection, and AIN	2004	2009
021	HIV-Infected Kids	120	Immunogenicity and Tolerability in HIV-infected 7-11 year-old children	2006	2009
024	Concomitant Vax	843	Co-administration with TdaP-IPV Immunogenicity of B60A material	2006	2007
025	Concomitant Vax	1040	Co-administration with TdaP, MnCV4 (Sanofi-Pasteur)	2006	2007
026	P005 Extension	350	Duration of efficacy of HPV 16 vaccine (through Year 8)	2006	2008

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# **CDC Safety Update from June 28th ACIP Meeting**

Preliminary Postlicensure Safety Data

# Vaccine Adverse Events Reporting System (VAERS)

- National post-licensure safety surveillance system jointly operated by CDC and FDA
- Spontaneous reporting system
  - Established in 1990
  - Submissions from clinicians, manufacturers, patients/parents, others
- Limitations (passive surveillance)
  - Underreporting
  - Stimulated reporting due to media attention
  - Lack of denominator data

# Vaccine Adverse Events Reporting System (VAERS): Quadrivalent HPV Vaccine through May 2007

- Total Reported    n=1763\*
- Sex
  - Females    96% (n=1700)
  - Unknown    3% (n=52)
  - Males       <1% (n=11)
- Age (yrs)
  - <9            1% (n=13)
  - 9-11          3% (n=57)
  - 12-18        39% (n=694)
  - 19-26        27% (n=474)
  - >26          4% (n=63)
  - Unknown     26% (n=462)

\*87% HPV4 alone (n=1539), 3% with Menactra® (n=44)

# Media Coverage

- Featured articles in Time, Wall Street Journal, Associated Press, Nature Medicine
- Press Releases from National Vaccine Information Center, Judicial Watch
- CDC/FDA response includes interviews with subject matter experts, preparation of Q&A on vaccine safety and efficacy
  - <http://www.cdc.gov/vaccines/vpd-vac/hpv/default.htm>
- Proposed state-based vaccination mandates of most interest, in addition to safety and efficacy concerns

# Summary and Conclusions

- Post licensure safety reporting has been vigorous to date, as is expected for a new vaccine that is attracting professional and media attention
  - Overall dose-adjusted adverse event reporting for GARDASIL is approximately 3 times what is seen on average for VAERS
- SAE reported rarely and no concerning pattern among serious events
  - Proportion of serious reports below overall average for VAERS (10-15%)
- Within a non-representative sample of managed care organizations most vaccine uptake is occurring among adolescents and pre-adolescents rather than young adults
  - Coverage data not yet available

# Summary and Conclusions

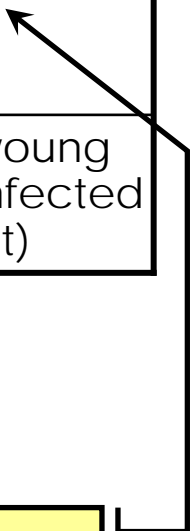
- Many reported events have high baseline rates in the absence of vaccination (e.g., syncope)
- As during trials, SAE of embolism and thrombosis attributable to OCP use have been detected
- Interpretation of some SAE confounded by concomitant vaccination and/or medication use, and by missing or incomplete data
  - Reported deaths do not appear to be causally related to vaccination

# Back-Up

# Population Definitions (Protocol 013 or 015)

Population	Description	Application	Relevance
RMITT-2	At Day 1, naïve to 14 HPV types and Pap test negative	Key analysis of Population Impact	HPV-naïve adolescents and young women
MITT-3	All subjects with efficacy follow-up	Supportive analyses	General population of young women (including HPV- infected at vaccination onset)

**RMITT-2 is not completely HPV-naïve  
(testing covers 12/17 cancer causing HPV types)**



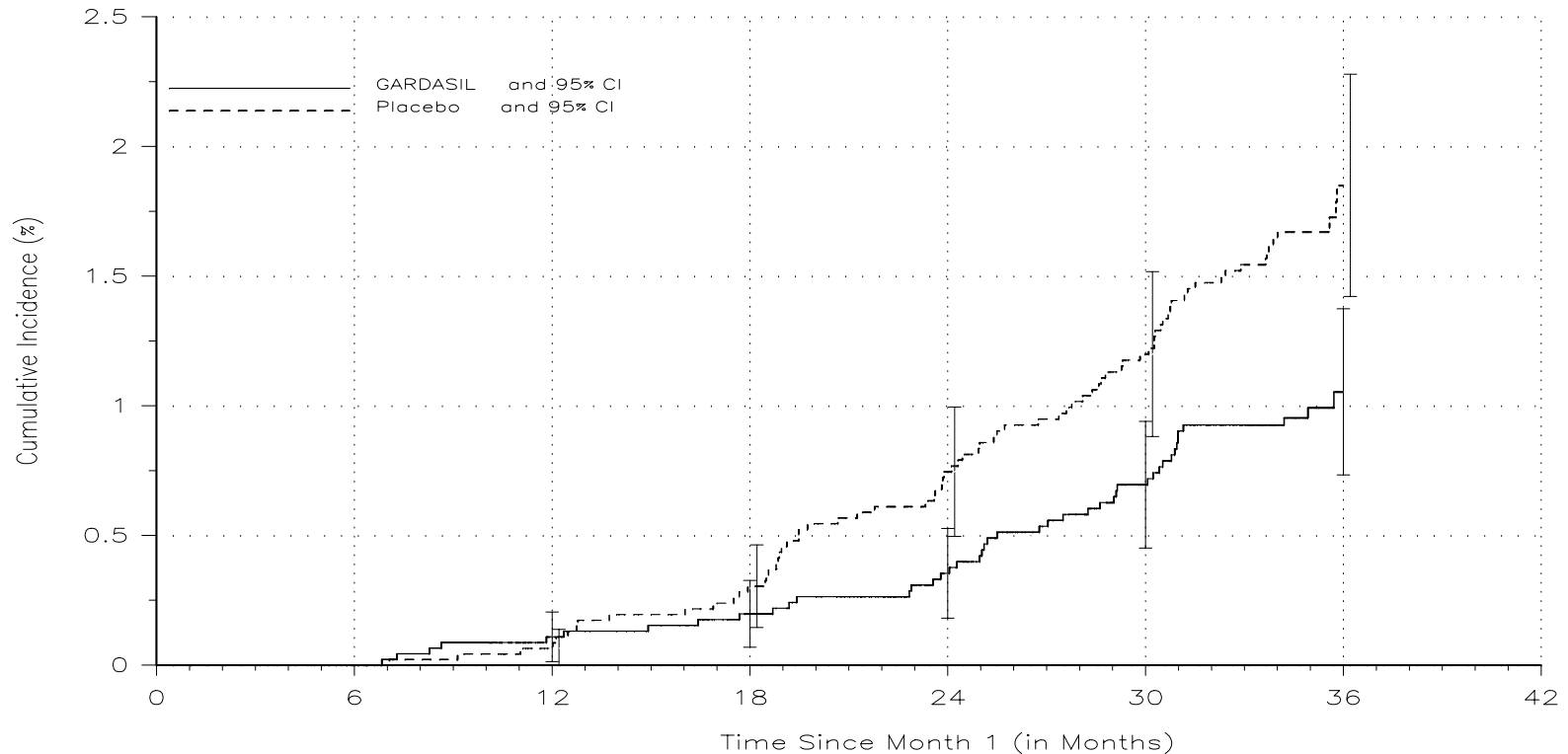
# Overall Population Impact at Year 3 Phase III Program

Endpoint	Analysis Population	Subjects With an Endpoint		% Reduction (95% CI)
		GARDASIL™	Placebo	
CIN 2/3 or AIS	RMITT-2	52	97	46 (24, 62)
	Any HPV Infection at Day 1 <sup>†</sup>	309	320	--
	MITT-3	361	417	14 (0.1, 25)
VIN 2/3 or VaIN 2/3	RMITT-2	6	25	76 (40, 92)
	Any HPV Infection at Day 1 <sup>†</sup>	21	27	--
	MITT-3	27	52	48 (16, 69)
CIN or AIS	RMITT-2	191	272	30 (15, 42)
	HPV Infection at Day 1 <sup>†</sup>	624	695	--
	MITT-3	815	967	16 (8, 24)
EGL	RMITT-2	49	189	74 (64, 82)
	Any HPV Infection at Day 1 <sup>†</sup>	164	226	--
	MITT-3	213	415	49 (40, 57)

<sup>†</sup> At Day 1: PCR(+) to HPV 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and/or 59; and/or Pap test  $\geq$ ASC-US; and/or anti-HPV 6, 11, 16, and/or 18 seropositive.

# Time to CIN 2/3 or AIS (Caused by Vaccine or Non-Vaccine Types)

RMITT-2 (Phase III) Population  
Approximates HPV-Naïve Girls/Women



Number of Subjects at Risk

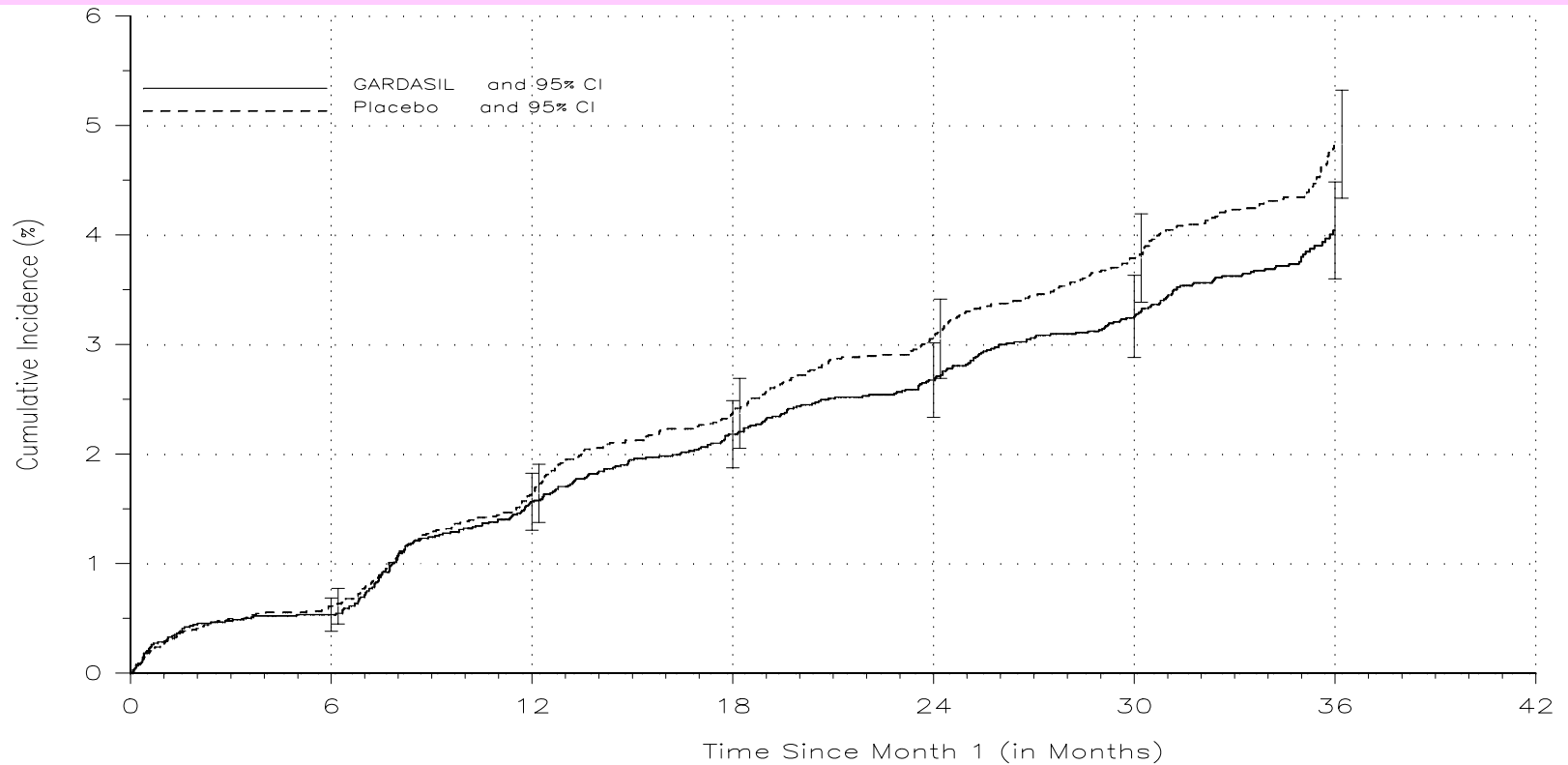
GARDASIL	4,616	4,606	4,541	4,507	4,404	4,317	1,410
Placebo	4,675	4,666	4,599	4,555	4,425	4,303	1,457

Graphs truncated at M36 (few subjects with follow-up at M42)

# Time to CIN 2/3 or AIS (Caused by Vaccine or Non-Vaccine Types)

## MITT-3

Approximates General Population (Including Women With HPV Infection at Day 1)



Number of Subjects at Risk

GARDASIL	8,817	8,723	8,508	8,377	8,114	7,895	2,516
Placebo	8,847	8,741	8,518	8,369	8,103	7,842	2,551

Graphs truncated at M36 (few subjects with follow-up at M42)

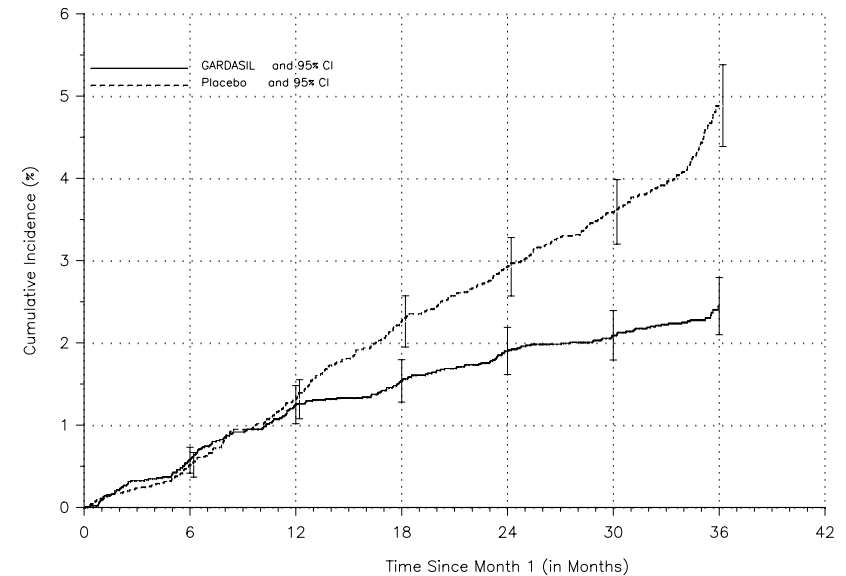
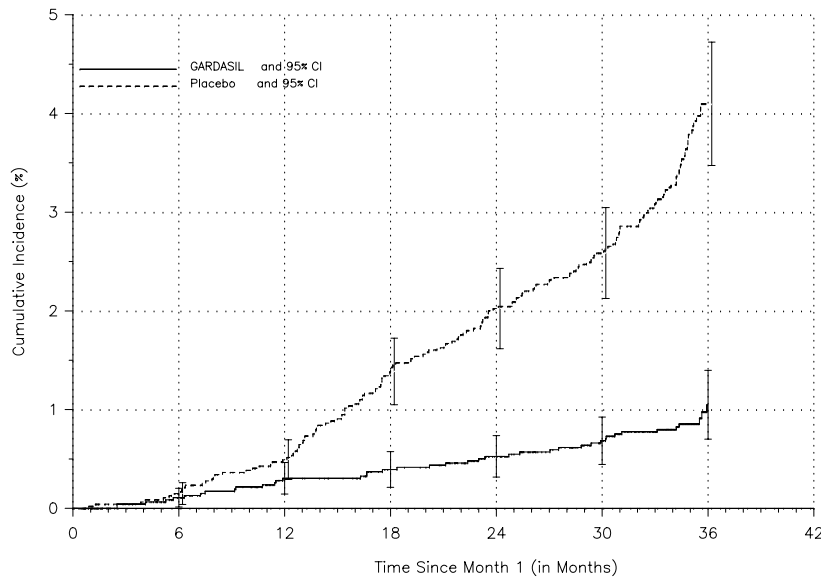
# Time to External Genital Lesions

## RMITT-2

Approximates  
HPV-Naïve Girls/Women

## MITT-3

Approximates  
General Population of Women



Graphs truncated at M36 (few subjects with follow-up at M42)

# Impact on Cervical Screening and Treatment Parameters

Population	Endpoint	Subjects With an Endpoint		% Reduction (95% CI)
		GARDASIL™	Placebo	
RMITT2	ASC-US (HC+)	213	289	26 (12, 39)
	ASC-H	48	75	36 (6, 56)
	LSIL	704	833	16 (7, 24)
	HSIL	18	35	48 (6, 72)
MITT3	ASC-US (HC+)	738	835	12 (3, 20)
	ASC-H	163	226	28 (12, 42)
	LSIL	1914	2134	12 (6, 17)
	HSIL	132	152	13 (-10, 32)
RMITT2	Colposcopy/Biopsy	500	636	22 (12, 30)
	Definitive Therapy	82	138	40 (21, 55)
MITT-3	Colposcopy/Biopsy	1790	1991	11 (5, 17)
	Definitive Therapy	466	582	20 (9, 29)

## HPV4 Events Reported to VAERS: Most Frequently Reported Symptoms

MedDRA Term*	N	%
Dizziness	221	13
Syncope	176	10
Injection site pain	170	10
Nausea	160	9
Pain	122	7
Rash	122	7
Pyrexia	117	6
Urticaria	111	6
Headache	104	6
Loss of consciousness	102	5

\*MedDRA – Medical Dictionary for Regulatory Activities – used for coding since January 2007

## HPV4 Events Reported to VAERS: Serious Adverse Events\*

- 94 serious reports (5% of total reports)
  - HPV4 given alone in 82% of reports (n=77)
  - Onset interval:
    - 42% (n=39) occurred on day of vaccination
    - Median onset interval 1 day after vaccination

\*Defined by CFR as involving hospitalization, death, disability, life threatening illness or other medically important conditions

## HPV4 Events Reported to VAERS: Most Common Symptoms Among SAE

MedDRA Term	N	%
Vomiting	13	14
Syncope	11	12
Pyrexia	10	11
Nausea	10	11
Headache	9	10

# Deaths Following HPV4

- CASE # 1: 12 year-old vaccinated with 1<sup>st</sup> dose of HPV4, 2<sup>nd</sup> doses of varicella and Hepatitis A vaccines March 1; died March 7<sup>th</sup> after presenting with ventricular tachycardia. Autopsy showed myocarditis. Presented to ED earlier same day with gastroenteritis; had respiratory illness ~ 2 weeks prior to death. PMH of mitral and aortic regurgitation and insufficiency.
- CASE # 2: 19 year-old vaccinated with 1<sup>st</sup> dose of HPV4 March 12<sup>th</sup>. Patient died March 26<sup>th</sup> from emboli; autopsy found large clots in right and left atria and dilated right ventricle. Cause of death listed as sudden cardiac death and pulmonary embolism. Patient was taking oral contraceptives (OCP) but did not smoke. Patient was exercising on field when she collapsed and began convulsing.

# Deaths Following HPV4

- CASE # 3: Minimal information received from a third party. History indicates that the vaccinee was taking OCP and that death from “blood clot” occurred 3 hours after vaccination.
- CASE # 4: 14 year-old received Tdap and HPV4 on January 2, 2007; then received HPV4 dose # 2 on March 2, 2007. Developed fever, sore throat and cough around March 4; diagnosed with influenza on March 5. Symptoms worsened and she was hospitalized on March 6 with initial diagnoses of pneumonia and ARDS; placed on ECMO. PMH includes hernia repair, migraines; started on Topamax® for migraines February 19, 2007. Labs: nasopharyngeal isolation of influenza B virus. MRSA cultured from multiple sites including blood and endotracheal aspirate. Died on March 16; cause of death multiorgan system failure due to influenza B viral sepsis with secondary staphylococcal infection.

# HPV4 Events Reported to VAERS: Guillain-Barre Syndrome (GBS) Reports

- 13 total reports: 2 have extremely limited information
- 11 reports among 13-26 year-olds (one 50 year-old, one age unknown)
- Co-administered vaccines (MCV4 – 6, None – 4, Unknown – 2)
- Onset intervals
  - 0-3 days: 4
  - 4-7 days: 1
  - 8-14 days: 4
  - >30 days: 2 (33, 42 days)
  - Unknown: 2

## HPV4 Events Reported to VAERS: SAE Involving Syncope

- 11 reports; 5 involved co-administration of at least one other vaccine
- Onset intervals following vaccination:
  - “immediate”: 2
  - <5 minutes: 1
  - 10 minutes: 2
  - Other intervals not specified
- Most commonly associated symptoms headache, fall, vomiting, dizziness and nausea
- 7 hospitalizations; diagnoses included vasovagal syncope, dehydration

# HPV4 Events Reported to VAERS: Thrombosis & Embolism

## Non-fatal reports

- Case # 1:
  - Female of unknown age vaccinated with HPV4 on unknown date
  - Patient subsequently developed blood clots in her legs
  - Non-serious report; additional information has been requested
- Case # 2:
  - 21 year-old female vaccinated with HPV4 on January 9, 2007
  - Traveled from March 3-10 on 2 flights (3 hours each)
  - March 6: calf pain that radiated to thigh
  - March 19: seen in ED for severe lower back pain
    - 2 large blood clots found in lungs (PE)
  - Started OCP for first time in February 2007
  - Genetic testing revealed multiple common risk factors for thromboembolism (e.g. prothrombin gene mutation)

## Background Rates of Venous

## Thromboembolism (VTE) Among Women

- Rate among OCP users (14-29 year-olds):
  - 21-31/100,000 woman years
  - Farmer, et al, Lancet, 1997
- Rate among OCP users of all ages:
  - 41/100,000 woman years
  - Farmer, et al, Lancet, 1997
- Rate among non-OCP, non-smokers (20-29 year-olds)
  - 3.3-4.0/100,000 woman years
  - Farley, et al, J Epi and Comm Health, 1998
- Rate among unknown risk status (20-29 year-olds)
  - 35-50/100,000 woman years
  - Silverstein, Arch Int Med, 1998

## HPV4 Events Reported to VAERS: Summary in 9-11 year-olds

- 57 reports
- 33% (n=19) occurred on day of vaccination; median onset interval 3 days after vaccination
- Most common coding terms rash, dizziness, pruritis, pyrexia, erythema
- 2 serious reports:
  - Stevens-Johnson Syndrome (SJS)
    - 5<sup>th</sup> hand report involving 11-12 year-old who developed SJS “1 month” after 1<sup>st</sup> dose; no information on concomitant medications
  - Other serious report involved rash, nausea