



GARDASIL™

**[Quadrivalent Human Papillomavirus
(Types 6, 11, 16, 18) Recombinant Vaccine]**

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MERCK

Research Laboratories

Presentation Outline

- Introduction
 - Epidemiology of HPV Infection
 - Product Profile – GARDASIL®
- Design of the Clinical Trials Program for GARDASIL®
- Clinical trial results for GARDASIL®

HPV Infection Causes Benign and Malignant Epithelial Dysplasia

- HPV is a potent carcinogen
 - Cervix
 - Vagina, vulva, anal canal
 - Penis
 - Tonsil, Pharynx, Larynx
- HPV causes benign tumors
 - Low grade cervical, vulvar, vaginal dysplasia
 - Genital warts
 - Recurrent Respiratory Papillomatosis

Cervical Cancer Screening

- In the U.S., Pap testing has reduced cervical cancer rates by 75%, but at high costs
 - 50 Million Pap tests annually to yield...
 - 3.5 Million Pap test abnormalities which result in...
 - 1.4 Million cases of CIN 1, and
 - 330,000 cases of CIN 2/3

And the total cost is \$4 to \$6 Billion (per year)

- Despite availability of screening, over 10,000 American women develop cervical cancer annually

World Health Organization; 2003: 1-74.

American Cancer Society: Cancer Facts and Figures 2005.

National Cancer Institute Fact Sheet. The Pap Test: Questions and Answers.

Schiffman M, et al Findings to date from the ALTS. Arch Pathol Lab Med 2003; 127: 946-9.

American Cancer Society: Cancer Facts and Figures 2006

Other HPV Diseases

- Genital warts:
 - Lifetime risk in men and women exceeds 10%
 - Significant physical symptoms
 - Depression, disruption of primary relationship
 - Treatment by ablation (painful)
 - 30% recurrence
- Recurrent Respiratory Papillomatosis (RRP)
 - Rapidly growing, benign laryngeal tumors that cause hoarseness and airway obstruction
 - Bi-modal distribution: young children, adults
 - On average, 4 surgeries per year to maintain airway patency

Munk C, et al Sex Transm Dis 1997; 24(10): 567-72.

Maw RD et al Int J STD AIDS 1998;9:571-8.

Conaglen MH et al Int J STD AIDS 2001;12:651-8.

Insinga RP et al Clin Infect Dis 2003;36:1397-403.

von Krogh G et al Sex Transm Inf 2000;76:162-8.

Derkey CS et al Otolaryngol Clin North Am 2000;33(5):1127-41.

GARDASIL® (Merck & Co., Inc.)

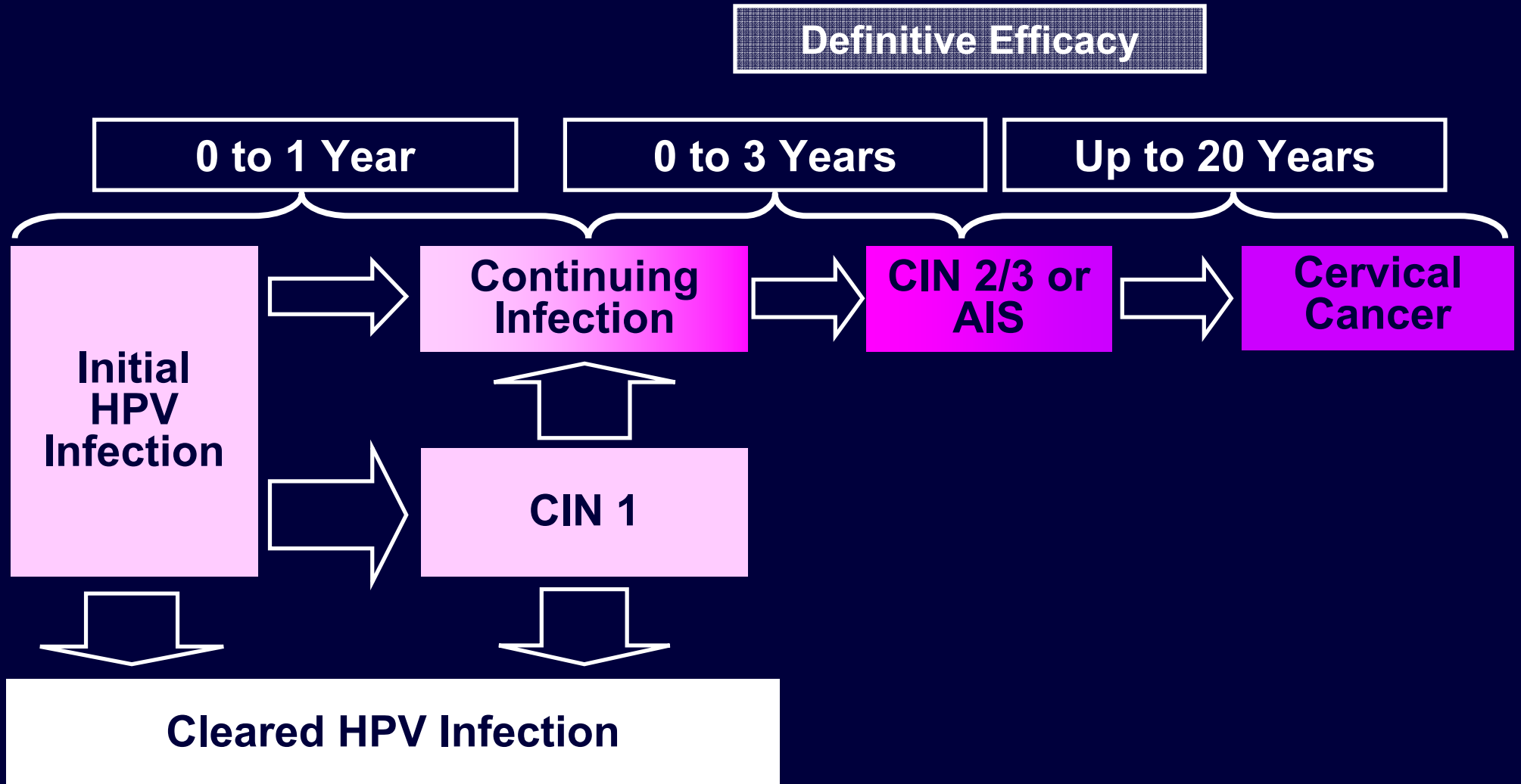
- VLPs manufactured in *S. cerevisiae*
- Aluminum Adjuvant 225 µg per dose
- 0.5 mL injection volume given in a 0, 2, 6 (month) dosing regimen

Type	Women	Men
16/18	70% of Cervical Cancer 70% of Anal/Genital Cancer 60% of CIN 2/3 25% of CIN 1	70% of Anal Cancer (MSM) 70% of AIN 2/3 (MSM) Prevention of infection (reduced transmission to women)
6/11	10 to 15% of CIN 1 90% of Genital Warts 90% of RRP	Prevention of infection (reduced transmission to women) 90% of Genital Warts 90% of RRP

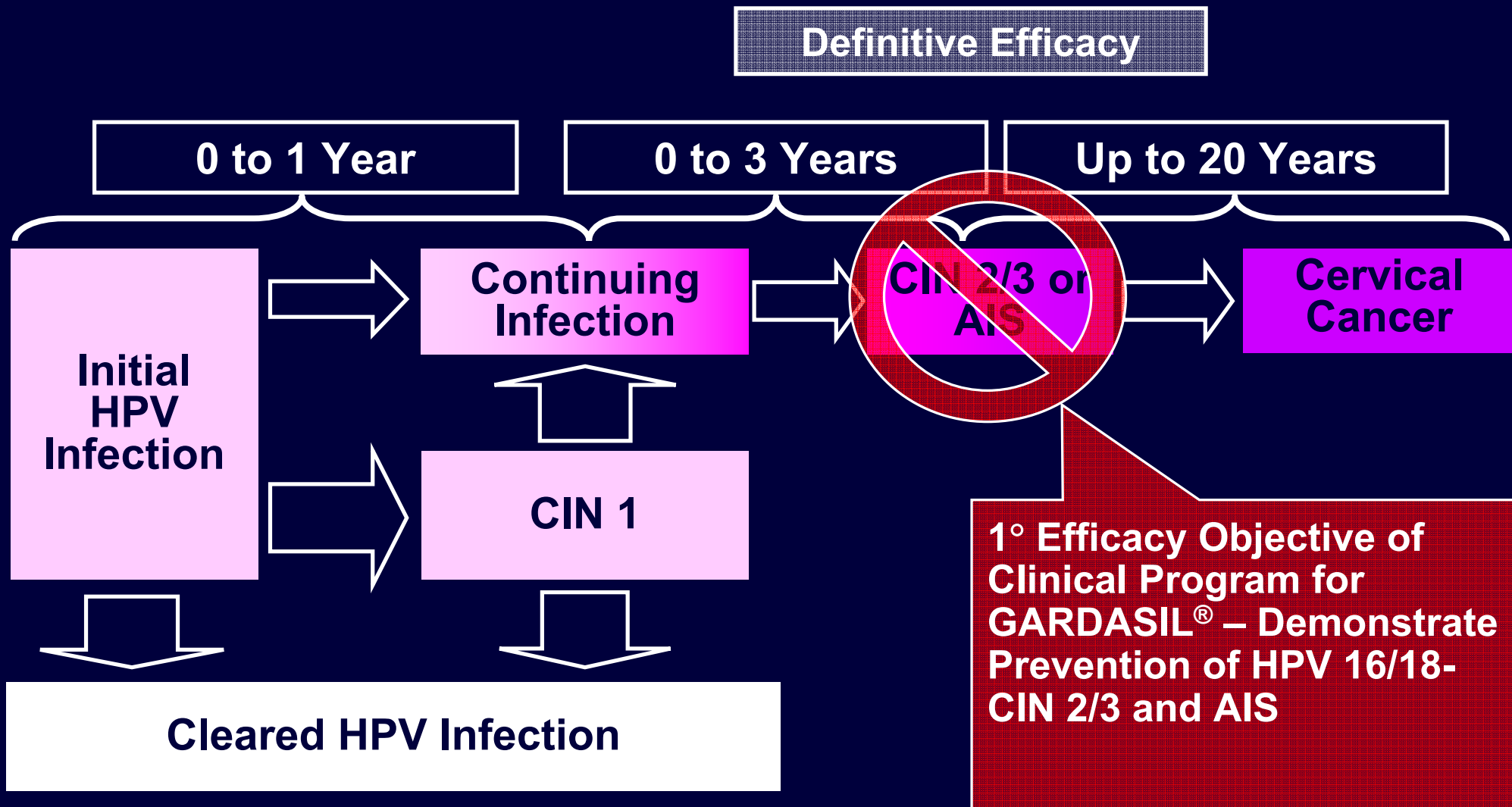
Objectives of Clinical Program for Gardasil®

1. Administration of Gardasil® will reduce the incidence of vaccine-type specific:
 - Cervical cancer (via CIN 2/3 + AIS)
 - CIN
 - External genital lesions
 - AIN and anal cancer
2. Administration of Gardasil® will reduce the overall incidence of HPV-related cervical and genital disease
3. Administration of Gardasil® will be effective and well tolerated in:
 - Adolescents aged 9 to <18 years (both genders)
 - Sexually active adults aged 18 to 45 (both genders)

Natural History of HPV Infection Guides Definition of Cervical Cancer Surrogates

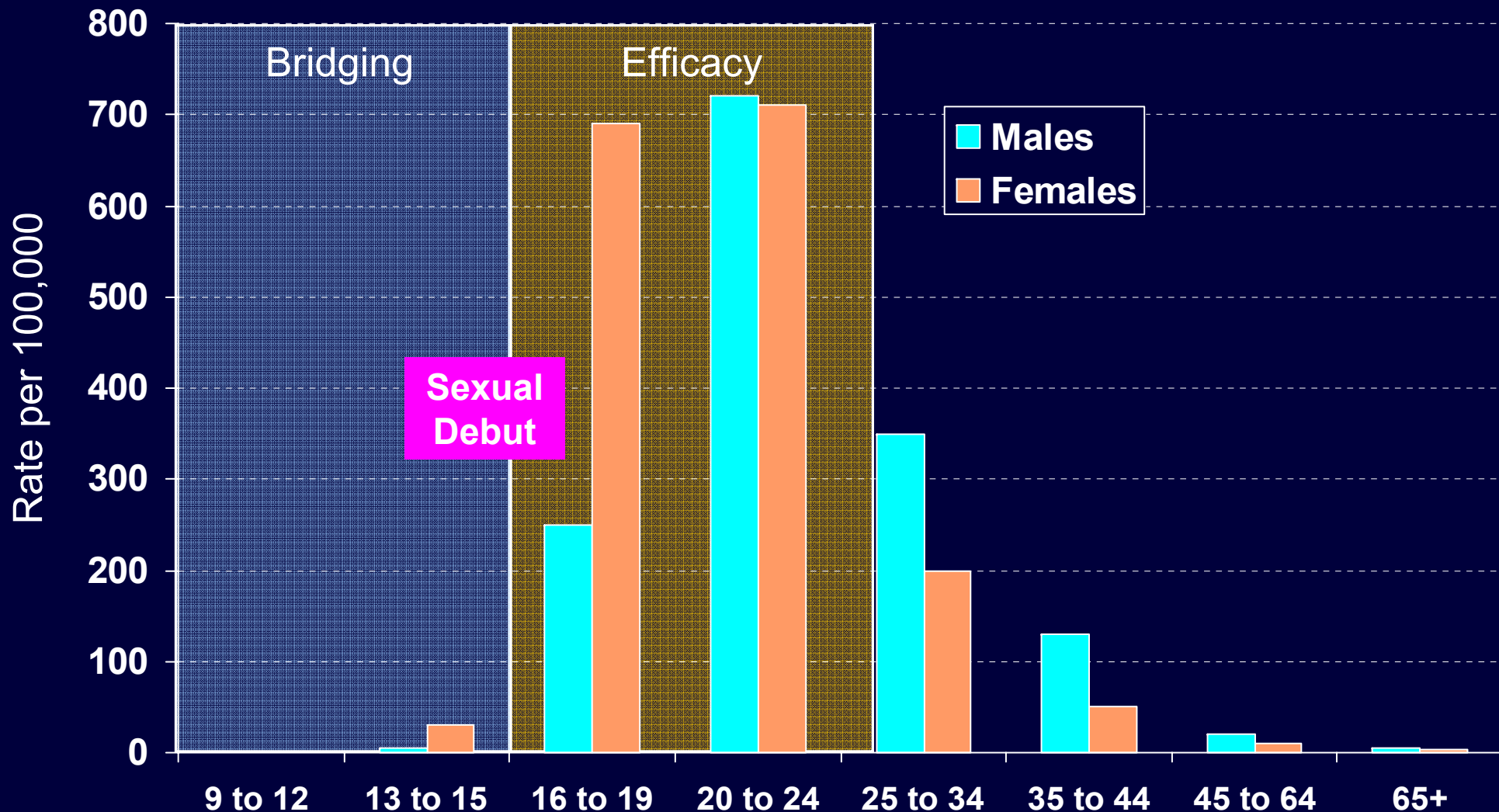


CIN 2/3 and AIS — Established Surrogate Markers for Cervical Cancer



HPV Risk by Age (Rates of First Diagnosis of Genital Warts in England + Wales)

CDR Weekly 2001; Vol 11(35)



Clinical Program for GARDASIL® (2003 and Later)

Protocol 005 (N=2,391)
16-23 year old women

Protocol 007 (N=1,155)
16-23 year old women

Yr 5 Immune Memory
Evaluation

FUTURE I (N=5,442)
16-23 year old women

Extension

FUTURE II (N=12,167)
15-26 year old women

Extension

Duration of Efficacy Registry Study
Nordic Region

Norwegian HPV Surveillance and
Disease Burden/Population Effectiveness Study

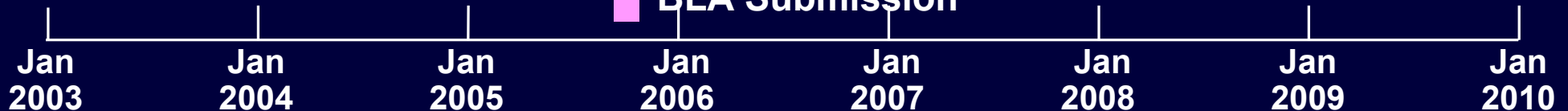
Ph III Adolescent Ig (N=4,800)
9-15 year olds, both genders

Adolescent Month
36 Extension

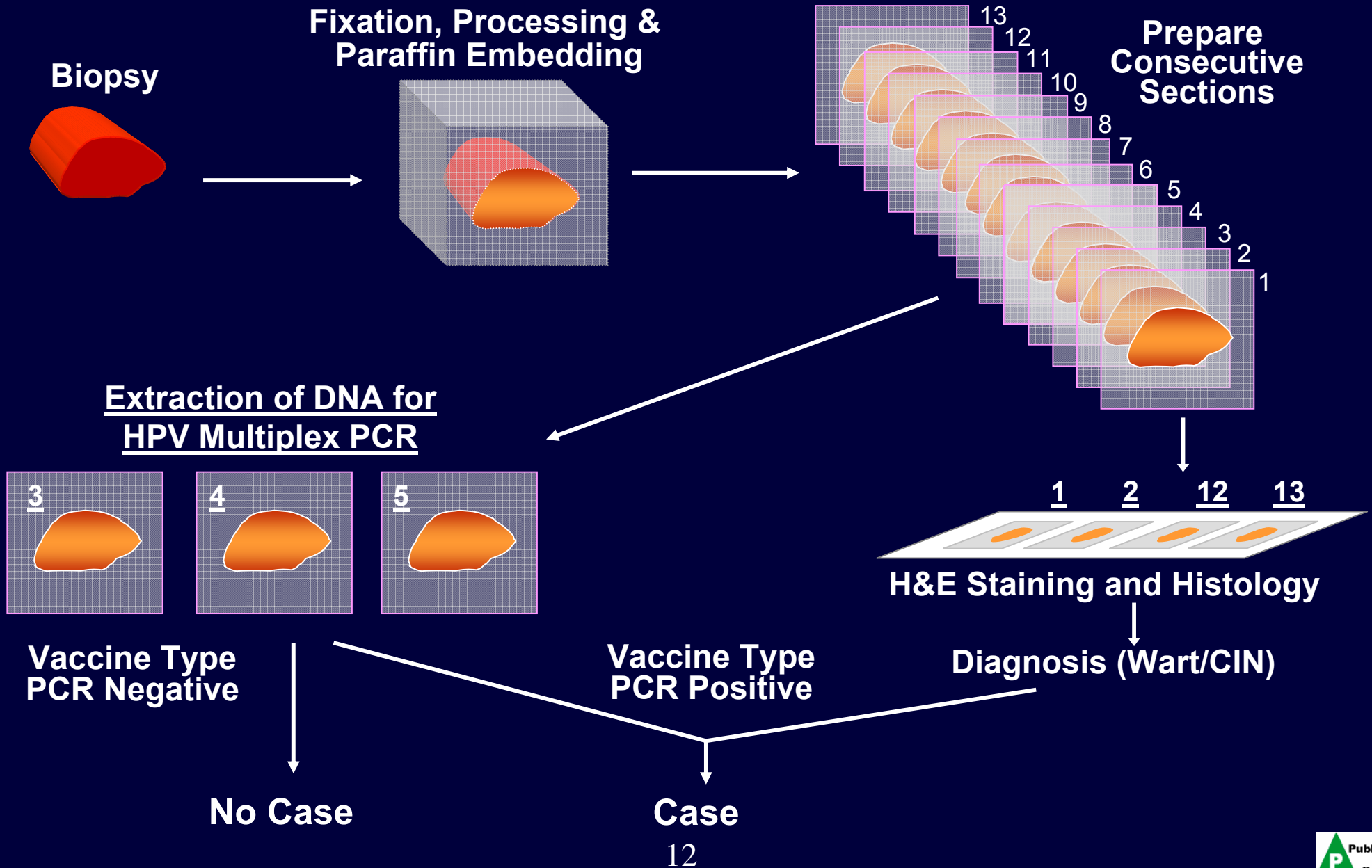
Efficacy Study
In Mid-Adult Women

Male Efficacy
Program

BLA Submission



Disease Endpoints



Phase III Efficacy Program

Day 1 Parameter	Total (N=20887)	Asia Pacific (N=748)	Europe (N=9181)	Latin America (N = 5666)	North America (N=5292)
Percent of total	100%	4%	44%	27%	25%
Mean Age	20	21	20	21	20
Non-virgin	94%	96%	92%	99%	93%
Mean Age at Sexual Debut (yrs)	17	18	17	17	17
Med. Lifetime # of Sex Partners	2	2	2	2	2
Past Pregnancy	23%	25%	7%	51%	16%
Using Hormonal Contraception	58%	50%	68%	46%	55%
Chlamydia (+)	4%	3%	3%	7%	3%
LSIL or HSIL	6%	5%	6%	7%	7%
HPV 6, 11, 16, or 18 (+)	27%	16%	25%	32%	25%
Naïve to all 4 types	73%	84%	75%	68%	75%

Prophylactic Efficacy Populations

Per-Protocol Efficacy (PPE) (~87% of Enrolled Subjects)

- HPV-naïve at Day 1
- Remain free of HPV infection during the course of vaccination
- Had follow-up visits
- No protocol violation
- Received all 3 doses
- Endpoint counting starting after Month 7

+

Additional Subjects (~8% of Overall Population)

- Infected during the course of vaccination
- Protocol violator
- Received <3 doses
- Had no follow-up visits
- Endpoints between Month 1 and Month 7

=

HPV-Naïve MITT (HN-MITT)[†] (~95% of Enrolled Subjects)

- Naïve to relevant HPV types at Day 1
- Had follow-up visits
- Case counting starting at Month 1

[†] In Clinical Study Reports, termed MITT-2.

HPV 16/18-Related Cervical Cancer [P005, P007, P013, P015]

Pop.	Endpoint	HPV Vaccine Cases	Placebo Cases	Efficacy	95% CI	p-Value
PPE	HPV 16/18-related CIN 2/3 or AIS	0	53	100%	93%, 100%	p<0.001
	HPV 16-related CIN 2/3 or AIS	0	44	100%	92%, 100%	
	HPV 18-related CIN 2/3 or AIS	0	14	100%	70%, 100%	
HN MITT	HPV 16/18-related CIN 2/3 or AIS	1	81	99%	93%, 100%	

Subjects are counted once per applicable row.

CI = Confidence interval

HN-MITT = HPV-naïve Modified Intention-to-Treat

HPV 16/18-Related Cervical Cancer in [Protocols 005, 007, 013, 015] HPV-Naïve MITT Population

Endpoint	HPV Vaccine Cases (N=9342)	Placebo Cases (N=9400)	Efficacy	95% CI
HPV 16/18-related CIN 3 or AIS	0	52	100%	93%, 100%
HPV 16/18-related CIN3	0	47	100%	92%, 100%
HPV 16/18-related AIS	0	9	100%	49%, 100%

Subjects are counted once per applicable row.

HPV 16/18-Related Vulvar and Vaginal Cancer in [P007, P013, P015] HPV-Naïve MITT Population

Endpoint	GARDASIL [®] Cases (N=8641)	Placebo Cases (N=8667)	Efficacy	95% CI
HPV 16/18-related VIN 2/3 or VaIN 2/3	0	24	100%	83%, 100%

HPV 6/11/16/18-Related CIN or AIS in Protocol 013

Pop.	Endpoint	GARDASIL [®] Cases	Placebo Cases	Efficacy	CI	p-Value
PPE	HPV 6/11/16/18- CIN or AIS	0	37	100%	87%,100%	p<0.001
	HPV 6-CIN/AIS	0	7	100%	30%,100%	
	HPV 11-CIN/AIS	0	3	100%	<0%,100%	
	HPV 16-CIN/AIS	0	22	100%	82%,100%	
	HPV 18-CIN/AIS	0	8	100%	41%,100%	
HN- MITT	HPV 6/11/16/18- CIN or AIS	2	57	97%	87%,100%	

Subjects are counted once per applicable row.

CI = Confidence interval (for PPE composite endpoint, 97.5% CI multiplicity adjusted for 2 primary endpoints; for remaining rows, 95% CI).

HPV 6/11/16/18-Related EGL Protocol 013

Pop.	Endpoint	GARDASIL® Cases	Placebo Cases	Efficacy	CI	p-Value
PPE	HPV 6/11/16/18-EGL	0	40	100%	88%,100%	p<0.001
	HPV 6-related EGL	0	23	100%	83%,100%	
	HPV 11-related EGL	0	10	100%	55%,100%	
	HPV 16-related EGL	0	10	100%	56%,100%	
	HPV 18-related EGL	0	3	100%	<0%,100%	
HN- MITT	HPV 6/11/16/18-EGL	3	59	95%	84%,99%	

Subjects are counted once per applicable row.

CI = Confidence interval (for composite endpoint, 97.5% CI multiplicity adjusted for 2 primary endpoints; for remaining rows, 95% CI).

Other Efficacy Findings

- Infection with one HPV type does not impact efficacy for other 3 HPV types
- Efficacy comparable across variations in dosing intervals (all subjects who received study vaccine regimen in a one year period were included in the per-protocol analyses)
- No impact of regional origin or ethnicity, sexual behavior, use or lack-of-use of hormonal contraceptives on efficacy
- Therapeutic efficacy:
 - If infected (PCR positive and seronegative) with a vaccine HPV type, modest reduction (trend) in disease due to that type
 - If infected (PCR positive and seropositive) with a vaccine HPV type, no reduction in disease due to that type

Prophylactic Population Impact Approximating HPV-Naïve Adolescents

- Research question:
 - If GARDASIL® is given prior to sexual debut, what is the magnitude of reduction in the overall risk for cervical cancer?
- Overall risk for cervical cancer due to:
 - vaccine HPV types (~70%)
 - non-vaccine HPV types (~30%)
- Requirement to answer this question:
 - Efficacy study starting in young adolescents – not feasible
 - Modeling the impact in a population of young women that is naïve to HPV types causing >95% of CIN
 - HPV 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59
- Definitive evaluation at end of the Phase III studies (2007)

Prophylactic Population Impact Preliminary Analysis

- Current (preliminary) evaluation
 - Negative to 4 vaccine HPV types
 - Unknown Status for 10 other HPV types
 - Instead: negative Pap test
- Negative Pap test
 - Excludes ~65% of CIN 2/3 and AIS present at Day 1 caused by non-vaccine HPV types
 - Unable to exclude subjects infected with non-vaccine HPV types at Day 1 who later develop CIN 2/3 or AIS
- Result – efficacy analysis includes CIN 2/3 or AIS cases in subjects who are HPV-infected at Day 1
 - Impacts efficacy findings, especially early in the study

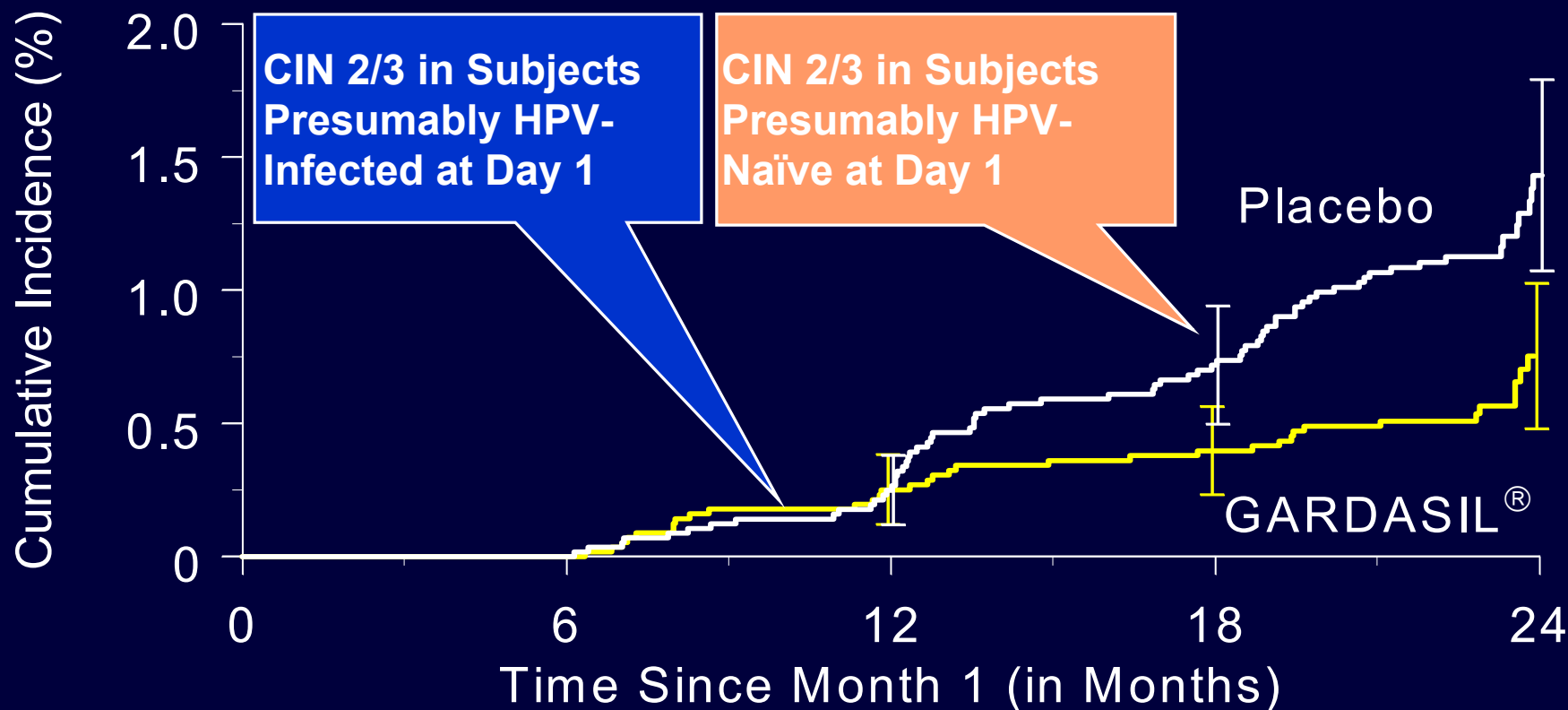
Prophylactic Population Impact Partially HPV-Naïve Population

- **Efficacy (Truly HPV-Naïve Population)**
 - (Efficacy for HPV 16/18-related CIN 2/3 and AIS) X (Proportion of overall CIN 2/3 and AIS caused by HPV 16/18)
 - Expected Efficacy = 99% X 0.55 = 54.5%
- **Efficacy (Partially HPV-Naïve Population) should be lower**

Endpoint	GARDASIL [®] Cases	Placebo Cases	Efficacy	95% CI
CIN 2/3 or AIS	59	96	38%	13%, 56%
CIN 2	42	74	43%	15%, 62%
CIN 3	28	50	43%	8%, 66%
AIS	0	5	100%	<0%, 100%

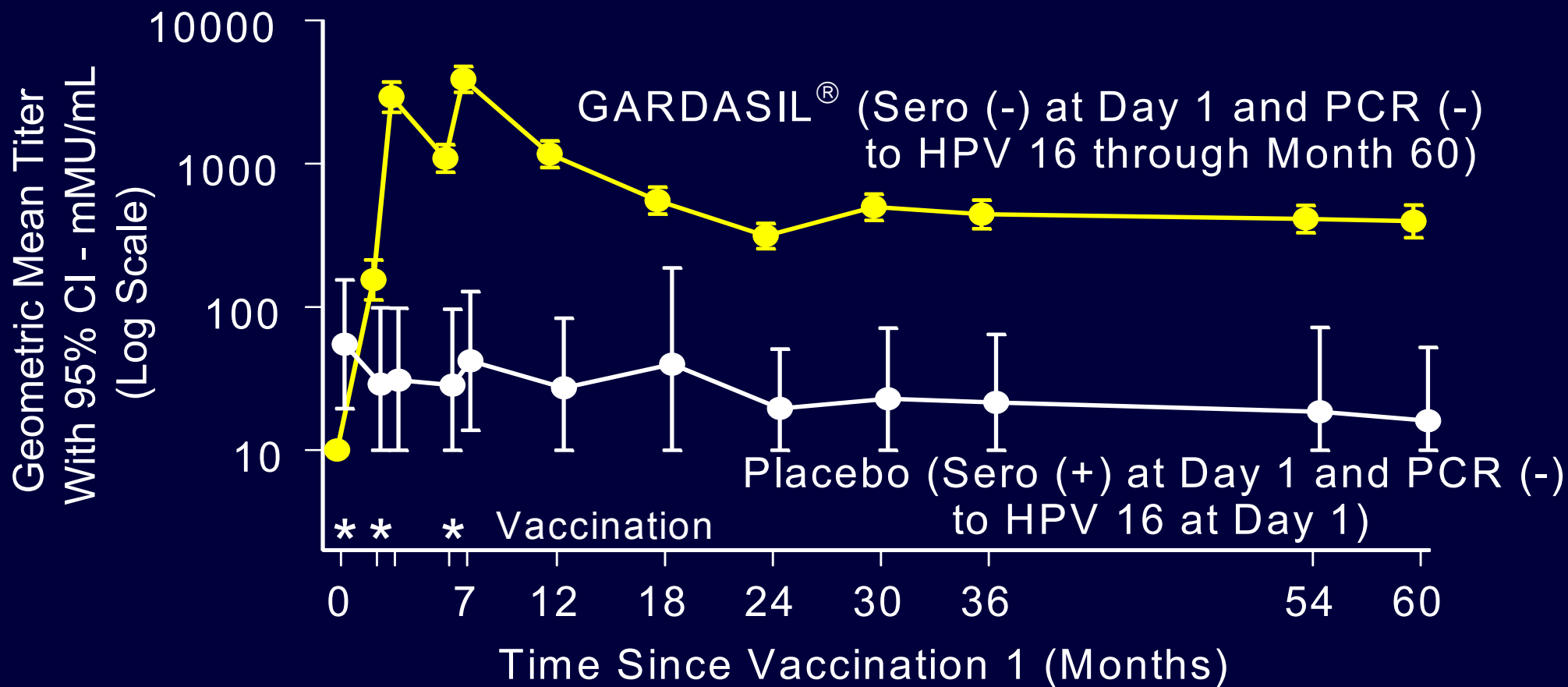
Time to Detection of CIN 2/3 or AIS (Regardless of Causal HPV Type)

Partially HPV-Naïve Population [P007, P013, P015]



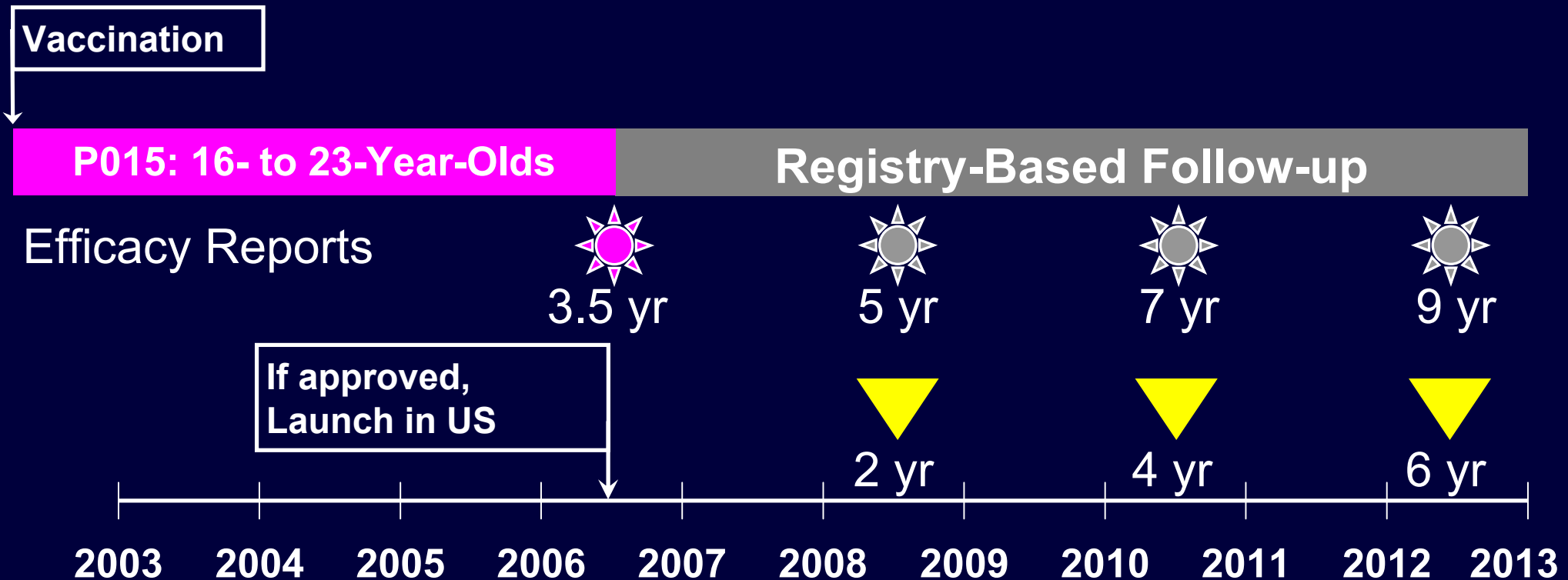
	Number of Subjects at Risk				
GARDASIL®	5638	5623	5474	5405	1873
Placebo	5701	5682	5537	5446	1958

Long-Term Persistence of Anti-HPV 16 cLIA Responses – Protocol 007



Adult Sentinel Cohort Provides Long-Term Effectiveness 3 Years Ahead of General Population

- Scandinavia has centralized mass-screening programs that allow for complete, long-term tracking and access to all Pap tests and biopsies
- 5800 study subjects and registries agreed to allow life-long follow-up



Efficacy: Conclusions

- Prophylactic administration of GARDASIL® is highly effective in preventing cervical and genital disease caused by HPV 6, 11, 16, and 18
- GARDASIL® reduces overall burden of HPV disease, as well as procedures used to diagnose/manage such disease
- Protective efficacy demonstrated for at least 3.5 years Postdose 3 (HPV 16) and at least 2.5 years postdose 3 (HPV 6, 11, 18)
- Sentinel cohorts have been set up to evaluate long-term efficacy well in advance of the general population

Safety Populations

All Subjects in All Studies (N = 27,004)

Monovalent HPV Vaccines or Placebo
(N = 3464)

Quadrivalent HPV Vaccine With Higher
VLP or Alum Doses Than GARDASIL[®]
(N = 552)

Quadrivalent HPV Vaccine With Lower
VLP Doses Than
GARDASIL[®] (N = 1524)

Safety Population

GARDASIL[®] or Placebo (N = 21,464)

- Serious Adverse Experiences
- Pregnancy Outcomes
- New Medical History

Detailed Safety Population

(N = 10,224)

- Vaccination Report Card (VRC)
(Nonserious AEs)

Protocol 015 Selected Sites

(N = 11,240)

- Spontaneous Reporting
(Nonserious AEs)

Overall Adverse Experience (AE) Summary Detailed Safety Population Days 1 to 15 Following Any Vaccination

Result	GARDASIL® (N=6160)		Placebo (N=4064)	
	n	(%)	n	(%)
Subjects with follow-up	6069		3994	
Number of Subjects				
with one or more AEs	5455	(89.9)	3416	(85.5)
injection-site AEs	5035	(83.0)	2932	(73.4)
systemic AEs	3591	(59.2)	2413	(60.4)
with serious AEs	37	(0.6)	26	(0.7)
with serious VR AEs	1	(0.0)	0	(0.0)
who died	1	(0.0)	1	(0.0)
Discontinued due to AE	11	(0.2)	6	(0.2)
Discon due to serious AE	2	(0.0)	2	(0.1)
Discon due to VR SAE	0	(0.0)	0	(0.0)

Maximum Temperatures Detailed Safety Population Days 1 to 5 Following Any Vaccination

Result	GARDASIL [®] (N=6160)	Placebo (N=4064)
Subjects with follow-up	6040	3981
Subjects With a Fever ($\geq 37.8^{\circ}\text{C}$)	11.4%	9.6%
$\geq 37.8^{\circ}\text{C}$ and $< 38.9^{\circ}\text{C}$	9.9%	8.6%
$\geq 38.9^{\circ}\text{C}$ and $< 39.9^{\circ}\text{C}$	1.3%	0.9%
$\geq 39.9^{\circ}\text{C}$	0.2%	0.2%

All temperatures were oral or oral equivalent

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

Subjects Given GARDASIL[®]
(Detailed Safety Population) by Gender + Age

No. of Subjects	18- to 26-Year Old Women N = 3697		9- to 17-Year Old Girls N = 1391		9- to 15-Year Old Boys N = 1071	
	n	(%)	n	(%)	n	(%)
With Follow-up	3640		1372		1056	
With 1 or more AEs	3370	(92.6)	1214	(88.5)	870	(82.4)
Injection-site AEs	3166	(87.0)	1111	(81.0)	757	(71.7)
Systemic AEs	2346	(64.5)	742	(54.1)	503	(47.6)
With serious AEs	26	(0.7)	7	(0.5)	4	(0.4)
With serious VR AEs	1	(0.0)	0	(0.0)	0	(0.0)
Died	1	(0.0)	0	(0.0)	0	(0.0)
Discon. due to AE	5	(0.1)	2	(0.1)	4	(0.4)

Summary

- Clinical HPV disease represents a major public health burden
- GARDASIL[®] is the first tool for primary prevention of HPV disease
- In clinical trials, prophylactic administration of GARDASIL[®] was highly effective in preventing cervical cancer, HPV-related vulvar and vaginal cancers, and genital warts
- There is strong evidence that the protective efficacy of GARDASIL[®] will be long lasting. A program to define the duration of efficacy of the vaccine is under way.
- GARDASIL[®] has an excellent safety profile