9-valent HPV (9vHPV) Vaccine Program Key Results

ACIP – 27-Feb-2014

Presenter: Alain Luxembourg, MD, PhD
Director, Clinical Research

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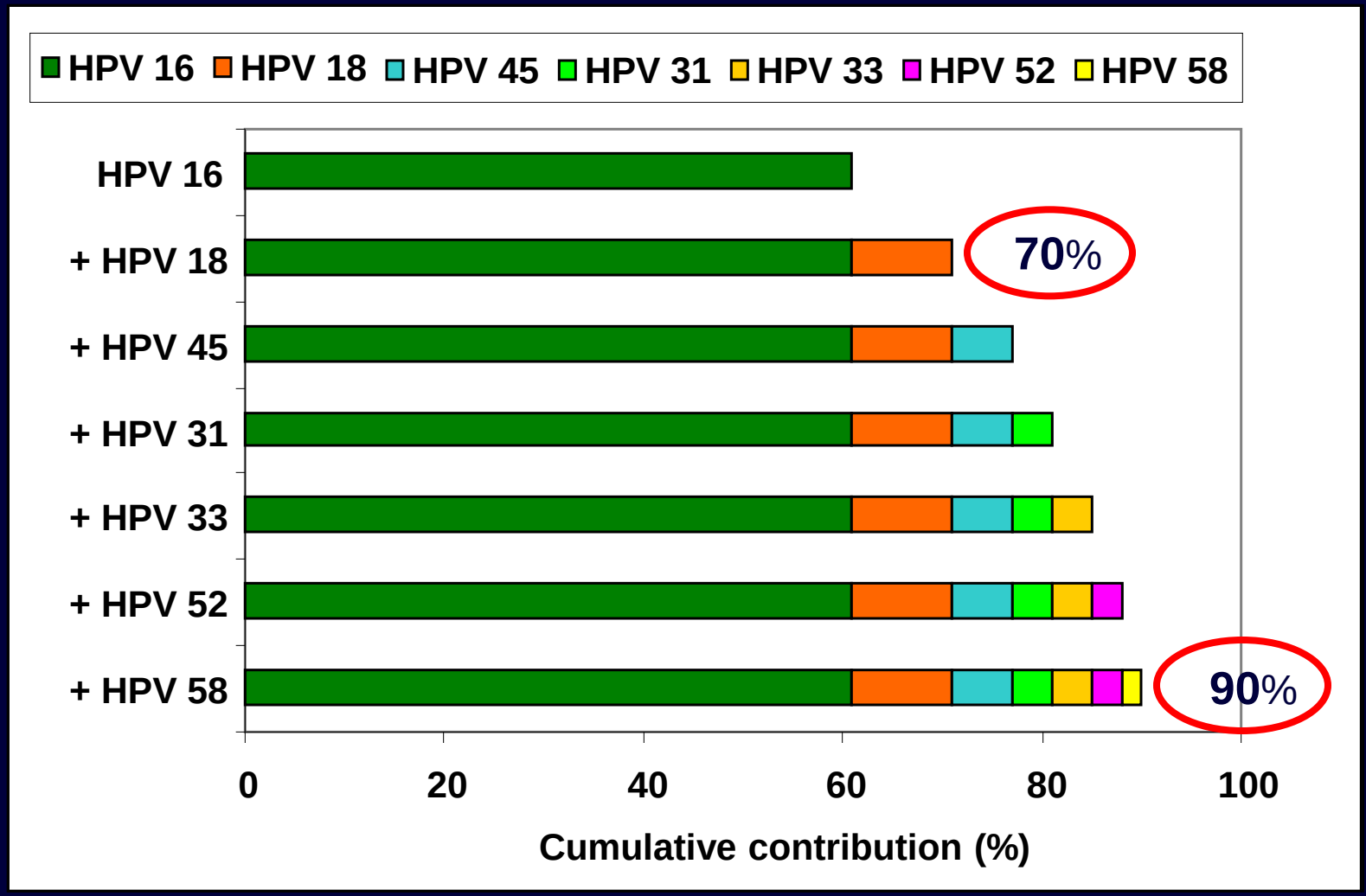
Abbreviations

Abbreviation	Definition
Vaccines	
• 9vHPV vaccine	Investigational 9-valent HPV vaccine
• qHPV vaccine	Licensed quadrivalent HPV vaccine (Gardasil)
Genital Lesions	
• CIN*	Cervical intraepithelial neoplasia
• VIN*	Vulvar intraepithelial neoplasia
• VaIN*	Vaginal intraepithelial neoplasia
**Grading: Grade 1=low-grade lesion; Grade 2/3=high-grade lesion*	

Relative Contribution of HPV Types in 9vHPV Vaccine to Cervical Cancers Worldwide



Among HPV-positive cervical cancers; based on de Sanjose et al. Lancet Oncol. 11:1048-56 (2010); Serrano et al. Infect Agent Cancer 7:38 (2012)

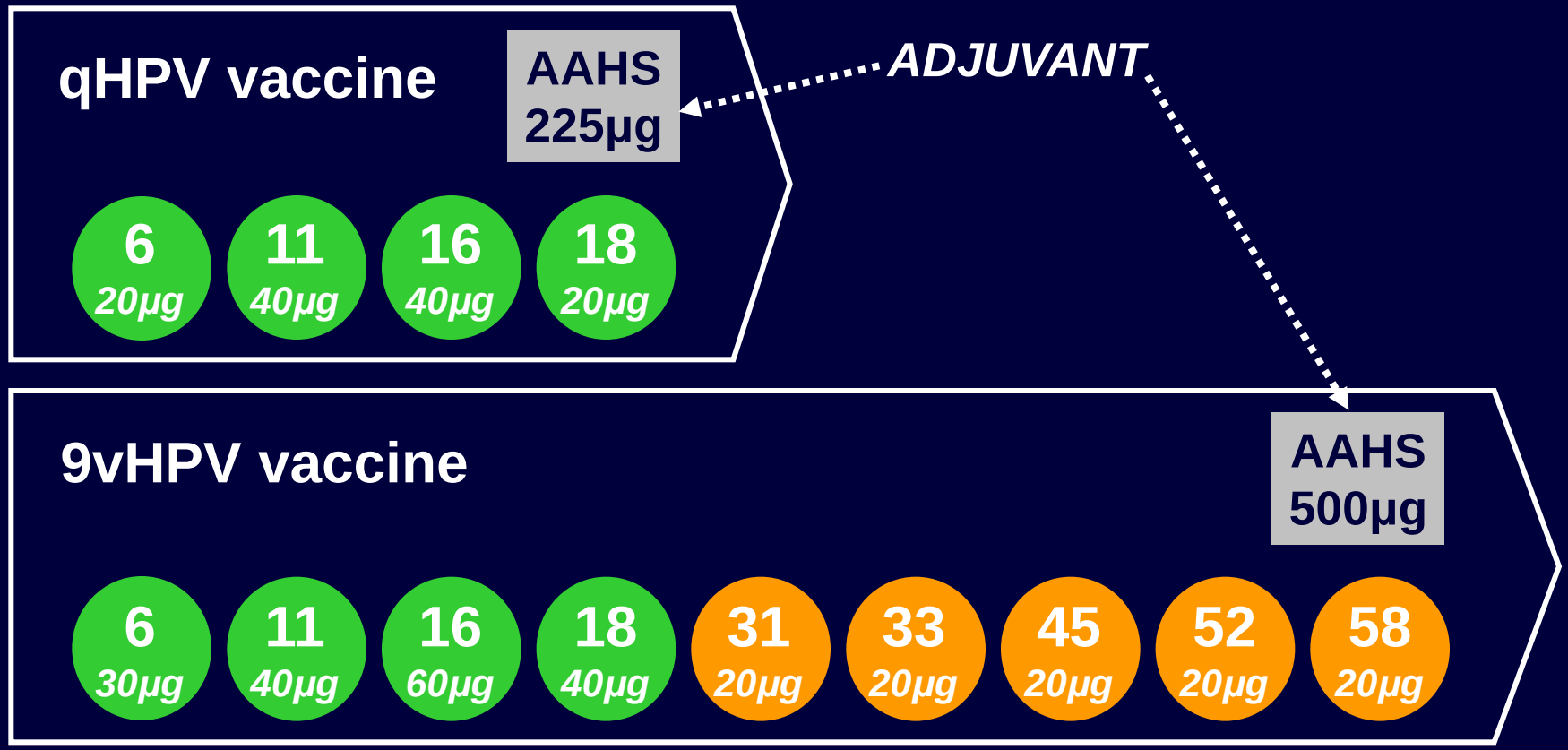
Relative Contribution of HPV Types in 9vHPV Vaccine to Cervical Disease Worldwide

Type of Lesion	6/11/16/18 Contribution	31/33/45/52/58 Contribution	Overall 9V Contribution
Cervical cancer*	70%	20%	90%
CIN2/3**	50%	30%	80%
CIN1**	25%	25%	50%

**Among HPV-positive cervical cancers; based on de Sanjose et al. 2010, Serrano et al. 2012*

***Estimates based on several meta analyses & results of analyses conducted among all lesions (HPV positive & negative) in placebo cohorts of several GARDASIL® clinical trials*

Comparison of 9vHPV Vaccine and qHPV Vaccine



AAHS =Amorphous aluminum hydroxyphosphate sulfate

Key Goals of the 9vHPV Vaccine Clinical Program

Topic	Goal
HPV 6/11/16/18	Provide similar level of protection as qHPV vaccine against infection/disease due to HPV 6/11/16/18
HPV 31/33/45/52/58	Highly protective against infection/disease due to HPV 31/33/45/52/58
Adolescents*	Non-inferior immunogenicity in adolescents vs. young women (immunobridging)
Safety	Acceptable safety/tolerability profile

**Adolescents cannot be directly assessed for efficacy (low exposure to HPV, constraints around performing genital examination in young adolescents)*

9vHPV Vaccine Studies – Initial Filing [1 of 2]: Pivotal Studies

STUDY RESULTS TO BE PRESENTED TODAY

Study	Population	N	Objective	Status
Pivotal efficacy study				
001	16-26 yo women	14000	Dose-ranging, efficacy, immunogenicity, safety	Completed Extension ongoing*
Immunobridging studies in adolescents				
002	9-15 yo boys & girls and 16-26 yo women	2800	Adult-to-adolescent immunobridging	Base study completed Extension ongoing*
009	9-15 yo girls	600	qHPV-to-9vHPV immunobridging	Completed

**Longer term safety, immunogenicity, efficacy/effectiveness*

9vHPV Vaccine Studies – Initial Filing [2 of 2]: Supportive Studies

STUDY RESULTS TO BE PRESENTED AT A FUTURE MEETING

Study	Population	N	Objective	Status
Concomitant use studies				
005	11-15 yo boys & girls	1240	Concomitant use: Menactra*, Adacel**	Completed
007	11-15 yo boys & girls	1040	Concomitant use: Repevax***	Completed
Study in prior qHPV vaccine recipients				
006	12-26 yo girls & women	900	Evaluation in prior qHPV vaccine recipients	Completed

**Meningococal vaccine; **Tdap vaccine; ***Tdap/polio vaccine*

Ongoing Phase III Study – Supplementary Filing

STUDY RESULTS TO BE PRESENTED AT A FUTURE MEETING

Study	Population	N	Objective	Status
Immunobridging studies in young men				
003	16-26 yo men (MSW and MSM) and 16-26 yo women	2500*	Women-to-men immunobridging	Ongoing**

**Including 1100 young women, 1100 MSW, and 300 MSM*

***Study results expected in 4Q2014*

Presentation Topics

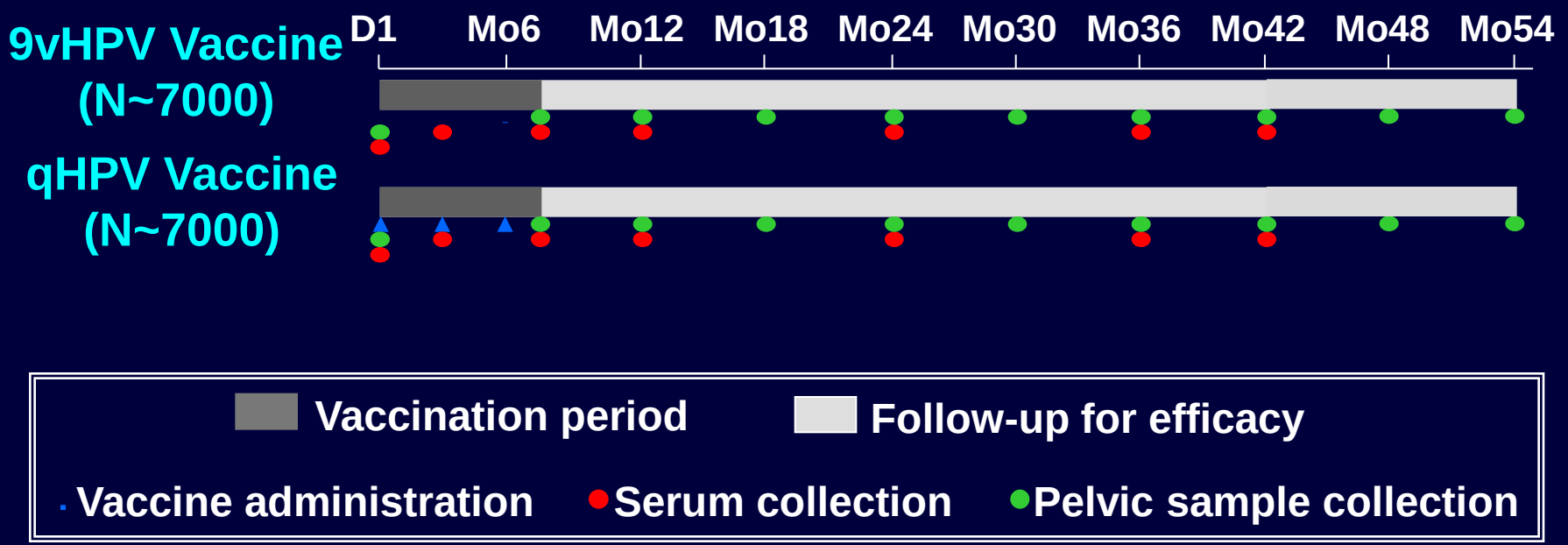
- Evaluation in young women (16-26 years of age)
  - **Protocol 001** (pivotal efficacy study)
    - Efficacy and immunogenicity
    - Safety
- Evaluation in adolescents (girls/boys, 9-15 years of age)
  - **Protocol 002** (adult-adolescent immunobridging)
    - Immunogenicity
    - Safety
  - **Protocol 009** (qHPV-9vHPV immunobridging)
    - Immunogenicity
    - Safety

Protocol 001 (Pivotal Efficacy Study): Study Design

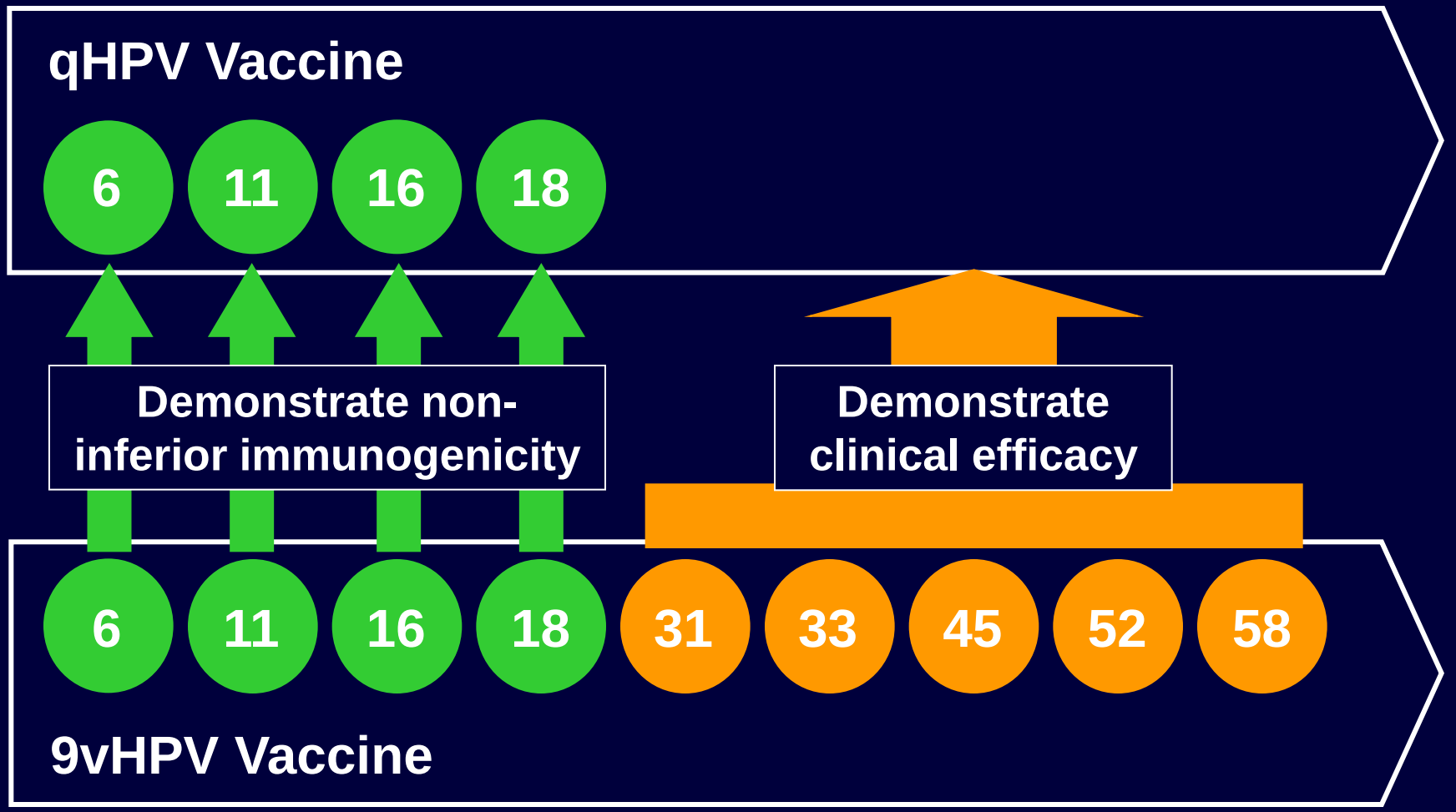
Study Population	**14,000 young women (16-26 years)** **Equally randomized to 9vHPV vaccine or qHPV vaccine**
Vaccination	**3-dose regimen (Day 1, Month 2, and Month 6)** **Double-blinded study: Subjects receive 9vHPV or qHPV vaccine**
Key Endpoints	**Efficacy: *Day 1 through end of study*** • **Genital swab (PCR) and Pap test every 6 months** • **Protocol-mandated triage if abnormal Pap test** **Immunogenicity: *primary endpoints: Day 1 and Month 7*** • **Anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 titers** **Safety: *Day 1 through end of study*** **Vaccination Report Card (VRC)-aided surveillance** **Serious Adverse Experiences (SAEs)**

Protocol 001: Efficacy Evaluation

- ~14,000 young women, age 16-26
- Up to 54 months follow-up
- Intensive screening (every 6 months)



Protocol 001 (Pivotal Efficacy Study): Primary Objectives

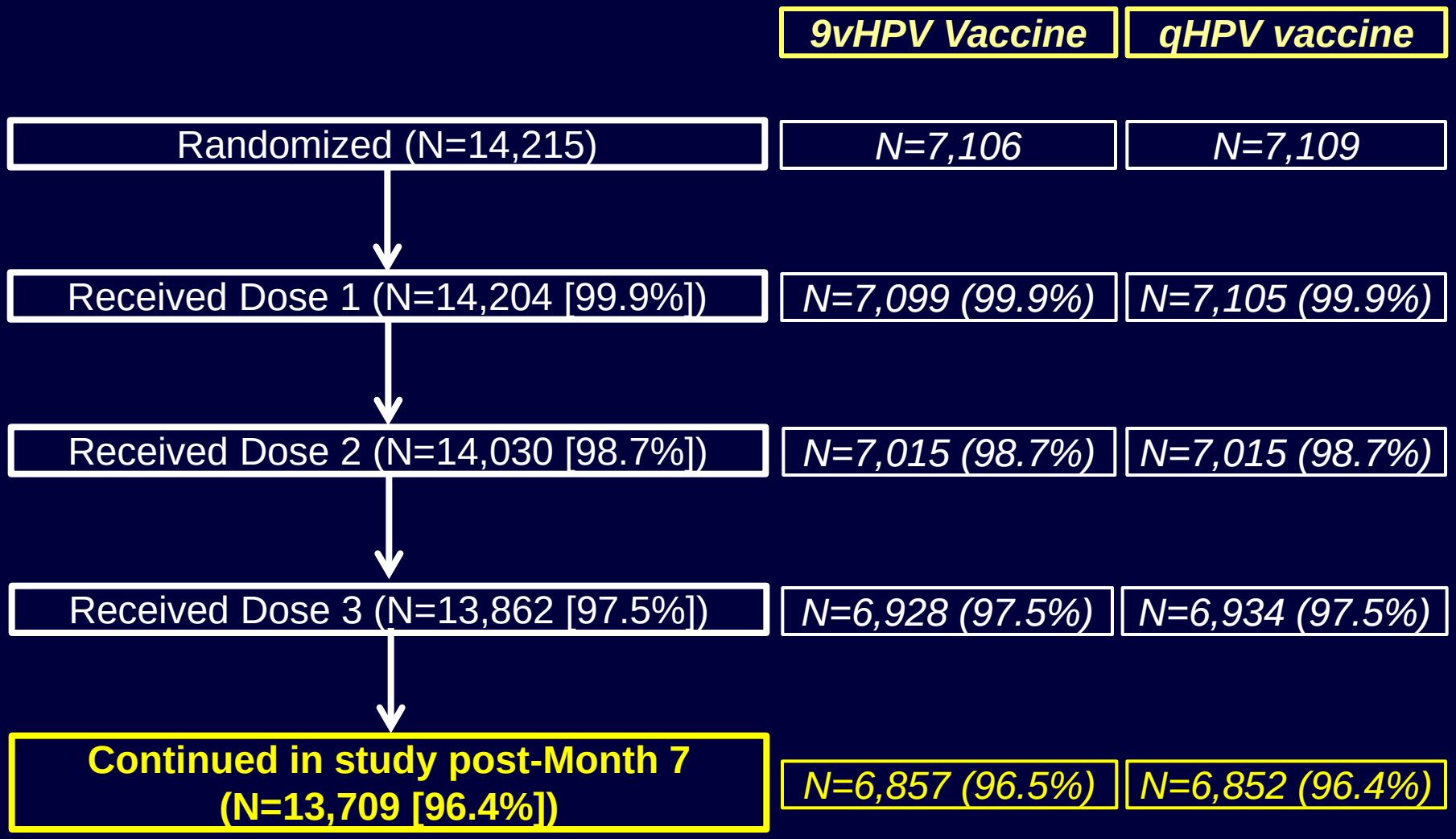


Primary Analysis Populations

Population	Definition
Per Protocol Efficacy (PPE)	• Sero(-) for the relevant HPV type at D1 • PCR(-) for the relevant HPV type on all swabs/biopsies from D1 through Mo7 • All 3 vaccinations administered within 1 year • No protocol violation ***Primary analysis population for efficacy***
Per Protocol Immunogenicity (PPI)	• Same criteria as PPE population • Received all 3 vaccinations within day ranges • Provided Month 7 serology within day ranges ***Primary analysis population for immunogenicity***

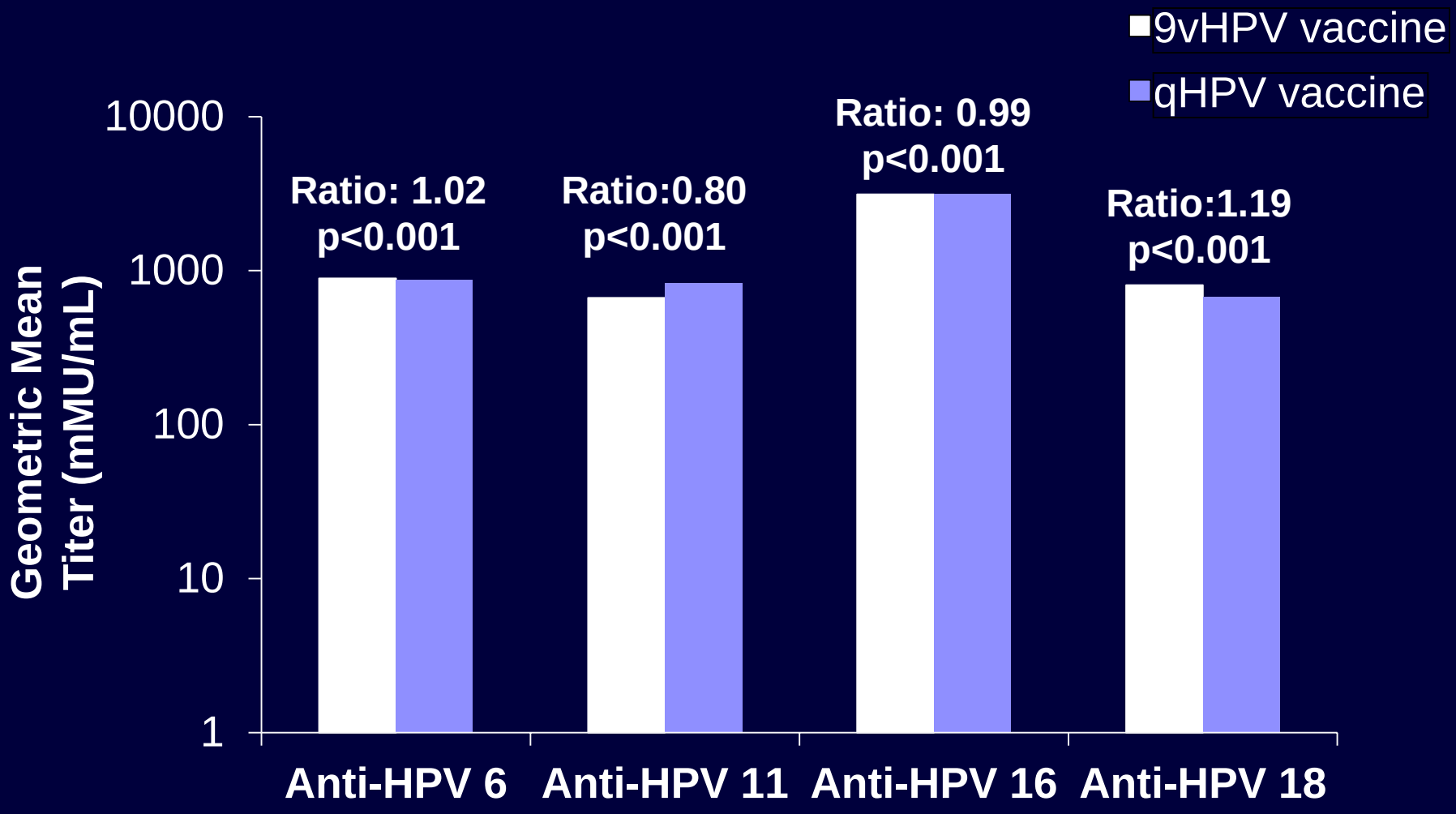
Same definitions as in the qHPV vaccine clinical program

Protocol 001: Subject Disposition



Protocol 001: Non-inferiority of Month 7 cLIA GMT in Women Administered 9vHPV Vaccine vs. Women Administered qHPV Vaccine

The non-inferiority criterion was met for all 4 HPV types (p<0.001)



Protocol 001: Non-inferiority of Month 7 cLIA Seroconversion Rates in Women Administered 9vHPV Vaccine vs. Women Administered qHPV Vaccine

The non-inferiority criterion was met for all 4 HPV types ($p<0.001$)

Anti-HPV cLIA Response	9vHPV Vaccine		qHPV Vaccine	
	n	%	n	%
Anti-HPV 6	3,393	99.8	3,975	99.8
Anti-HPV 11	3,395	100	3,982	99.9
Anti-HPV 16	4,032	100	4,062	100
Anti-HPV 18	4,539	99.8	4,541	99.7

Efficacy Against HPV 31/33/45/52/58 [1 of 3]

(Cervical/Vulvar/Vaginal Disease, Persistent Infection)

Per Protocol Efficacy Population

Endpoint	9vHPV Vaccine No. of cases/n	qHPV Vaccine No. of cases/n	Efficacy (95% CI)
≥CIN2, VIN2/3, VaIN2/3	1 / 6016	30 / 6017	**96.7% (80.9, 99.8)**
All CIN, VIN, VaIN	3 / 6016	103 / 6017	**97.1% (91.8, 99.2)**
6-month persistent infection	35 / 5939	810 / 5953	**96.0% (94.4, 97.2)**

Efficacy Against HPV 31/33/45/52/58 [2 of 3]
(Cervical Disease vs. Vulvar/Vaginal Disease)
Per Protocol Efficacy Population

Endpoint	9vHPV Vaccine No. of cases/n	qHPV Vaccine No. of cases/n	Efficacy (95% CI)
≥CIN2	1 / 5948	27 / 5943	**96.3% (79.5, 99.8)**
All CIN	2 / 5948	88 / 5943	**97.7% (92.2, 99.6)**
≥VIN2/3, VaIN2/3	0 / 6009	3 / 6012	**100% (-71.5, 100)**
All VIN, VaIN	1 / 6009	16 / 6012	**93.8% (61.5, 99.7)**

Efficacy Against HPV 31/33/45/52/58 [3 of 3]
(Invasive Procedures)
Per Protocol Efficacy Population

Endpoint	9vHPV Vaccine No. of cases/n	qHPV Vaccine No. of cases/n	Risk Reduction (95% CI)
Biopsy	7 / 6016	222 / 6017	**96.9% (93.6, 98.6)**
External Genital Biopsy	2 / 6009	22 / 6012	**90.9% (65.7, 98.5)**
Cervical Biopsy	6 / 6012	208 / 6014	**97.2% (93.9, 98.8)**
Definitive Therapy (Cervical, Non-ablative)*	4 / 6012	32 / 6014	**87.5% (65.7, 96.0)**

***e.g., loop electrosurgical excision procedure (LEEP), conization.*

Protocol 001: Vaccine-Related Adverse Experience (AE) Summary

(Days 1 to 15 Following Any Vaccination)

Subjects	9vHPV Vaccine (N=7,071) n (%)	qHPV Vaccine (N=7,078) n (%)
All vaccine-related* AEs	**6,519 (92.2)**	**6,200 (87.6)**
Injection-site	6,422 (90.8)	6,023 (85.1)
Systemic	2,086 (29.5)	1,929 (27.3)
Discontinued** due to a vaccine-related AE	5 (0.1)	3 (0.0)
With serious vaccine-related* AEs	**2 (0.0)**	**1 (0.0)**
Discontinued** due to a serious vaccine-related AE	1 (0.0)	0 (0.0)
	0 (0.0)	0 (0.0)

**Determined by the investigator to be related to the vaccine **Study medication withdrawn*

Protocol 001: Injection Site AEs

(Days 1 to 5 Following Any Vaccination)

Adverse event	9vHPV Vaccine (N=7071) %	qHPV Vaccine (N=7078) %	% Risk Difference (95% CI)	p-Value
Injection-site erythema*	34.0	25.6	8.5 (7.0; 10.0)	<0.001
Injection-site pain*	89.9	83.5	6.4 (5.3; 7.5)	<0.001
Injection-site swelling*	40.0	28.8	11.3 (9.7; 12.8)	<0.001

*Most injection-site AEs were of mild or moderate intensity in both vaccine groups.

Protocol 001: Systemic Vaccine-Related* AEs (Incidence ≥2%)

(Days 1 to 15 Following Any Vaccination)

Injection-site AE	9vHPV Vaccine (N=7,071)	qHPV Vaccine (N=7,078)
	n (%)	**n (%)**
Headache	1,031 (14.6)	969 (13.7)
Pyrexia	357 (5.0)	301 (4.3)
Nausea	311 (4.4)	261 (3.7)
Dizziness	211 (3.0)	197 (2.8)
Fatigue	166 (2.3)	150 (2.1)

**Determined by the investigator to be related to the vaccine.*

Protocol 001: Vaccine-Related* Serious Adverse Events

Relative Day of Onset	Adverse Event	Hospitalized	Duration	Outcome	Discontinued Vaccine
9vHPV Vaccine Group					
1d PD1	Allergy to vaccine	No	23 hours	Resolved	Yes
2d PD3	Pyrexia	No	2 days	Resolved	No
qHPV Vaccine Group					
2d PD2	Headache	Yes (1 day)	1.8 months	Resolved	No
18d PD3	Hypoesthesia	No	1.7 years	Resolved	No

**Determined by the investigator to be related to the vaccine.*

Protocol 001: Conclusions

Efficacy

- HPV types 6, 11, 16, 18: Non-inferior immune response
- HPV types 31, 33, 45, 52, 58: ~97% reduction in disease

Safety

- Generally well tolerated in >7,000 young women
- Adverse experiences profile generally comparable between 9vHPV vaccine and qHPV vaccine
  - Higher frequency of injection-site AEs with 9vHPV vaccine
  - Most were of mild or moderate intensity

Protocol 002 (Adult-Adolescent Immunobridging): Objectives

Immunogenicity

- To demonstrate non-inferior immunogenicity of 9vHPV vaccine in adolescents (9-15 years of age) vs. young women (16-26 years of age; *i.e., the population used to establish 9vHPV vaccine efficacy*)

Safety

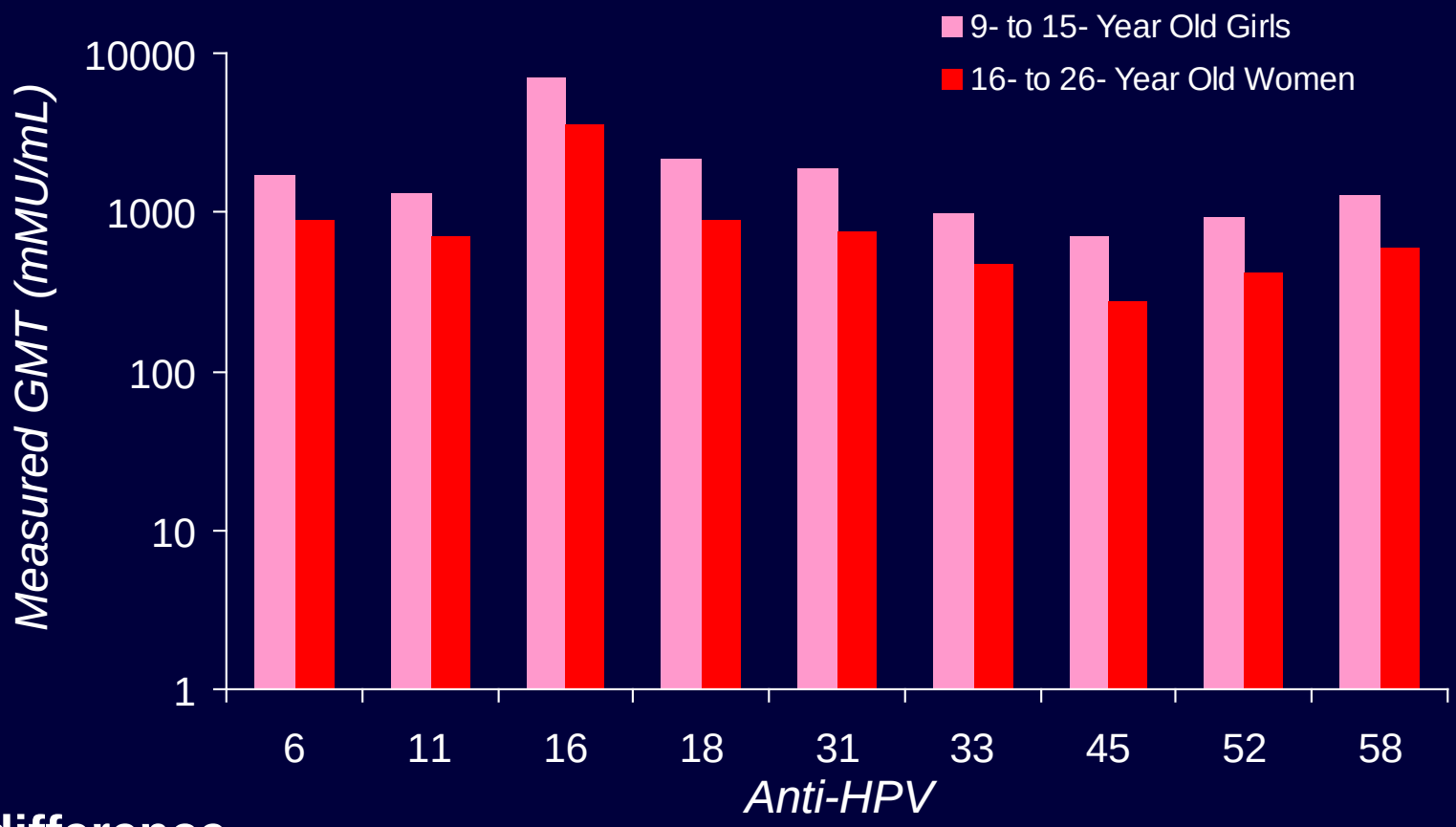
- To evaluate the safety/tolerability of the 9vHPV vaccine in adolescent boys and girls and young women

Protocol 002: Study Design

Study Population	**1800 girls (9-12 years: ~1200; 13-15 years: ~600)** **600 boys (9-12 years: ~400; 13-15 years: ~200)** **400 young women (16-26 years)**
Vaccination	**Day 1, Month 2, and Month 6** **Open label study: All subjects receive 9vHPV vaccine**
Key Endpoints	**Immunogenicity: *Day 1 and Month 7*** **Anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 titers** **Safety: *Day 1 through Month 12*** **Vaccination Report Card (VRC)-aided surveillance** **Serious Adverse Experiences (SAEs)**

Protocol 002: Non-inferiority of Month 7 cLIA GMT in Girls vs. Women After Vaccination with 9vHPV Vaccine

The non-inferiority criterion was met for all 9 HPV types (all p<0.001)



Fold difference (Girls/Women):	**1.9**	**1.8**	**2.0**	**2.4**	**2.5**	**2.1**	**2.6**	**2.2**	**2.2**

Protocol 002: Non-inferiority of Month 7 cLIA Seroconversion in Girls vs. Women After Vaccination with 9vHPV Vaccine

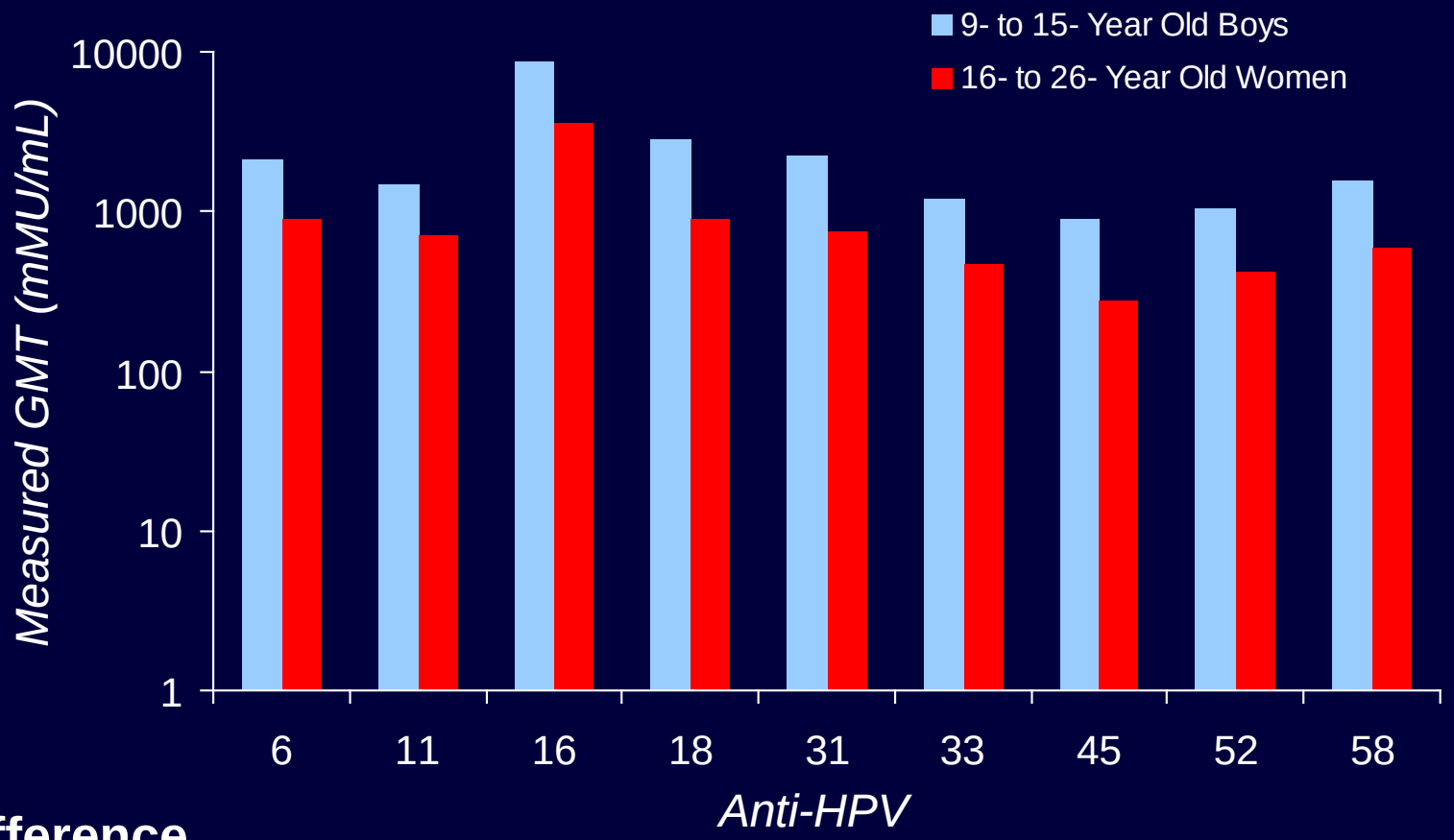
The non-inferiority criterion was met for all 9 HPV types (all p<0.001)

	9vHPV Vaccine			
	Girls (N = 646)		Women (N = 468)	
Anti-HPV cLIA Response	n	Seroconversion (%)	n	Seroconversion (%)
HPV 6	517	**99.8**	328	**99.7**
HPV 11	517	**100**	332	**100**
HPV 16	529	**100**	329	**100**
HPV 18	531	**99.8**	345	**99.7**
HPV 31	522	**100**	340	**99.7**
HPV 33	534	**100**	354	**99.7**
HPV 45	534	**99.8**	368	**99.5**
HPV 52	533	**100**	337	**99.7**
HPV 58	531	**100**	332	**100**

n = number of subjects contributing to the analysis

Protocol 002: Non-inferiority of Month 7 cLIA GMT in Boys vs. Women After Vaccination with 9vHPV Vaccine

The non-inferiority criterion was met for all 9 HPV types (all p<0.001)



Fold difference (Boys/Women):	**2.3**	**2.1**	**2.5**	**3.2**	**3.0**	**2.6**	**3.3**	**2.5**	**2.7**

Protocol 002: Non-inferiority of Month 7 cLIA Seroconversion in Boys vs. Women After Vaccination with 9vHPV Vaccine

The non-inferiority criterion was met for all 9 HPV types (all p<0.001)

Anti-HPV Response	9vHPV Vaccine			
	Boys (N = 666)		Young Women (N = 468)	
	n	Seroconversion (%)	n	Seroconversion (%)
HPV 6	559	**99.8**	328	**99.7**
HPV 11	559	**100**	332	**100**
HPV 16	569	**100**	329	**100**
HPV 18	567	**100**	345	**99.7**
HPV 31	564	**100**	340	**99.7**
HPV 33	567	**100**	354	**99.7**
HPV 45	570	**100**	368	**99.5**
HPV 52	568	**100**	337	**99.7**
HPV 58	566	**100**	332	**100**

n = number of subjects contributing to the analysis

Protocol 002: Vaccine-Related AE Summary (Days 1 to 15 Following Any Vaccination)

Subjects	Girls N=1923 n (%)	Boys N=662 n (%)	Young Women N=466 n (%)
All vaccine-related* AEs	**1614 (83.9)**	**500 (75.5)**	**406 (87.1)**
Injection-site	1577 (82.0)	483 (73.0)	398 (85.4)
Systemic	401 (20.9)	144 (21.8)	121 (26.0)
Discontinued** due to a vaccine-related AE	0 (0.0)	1 (0.2)	0 (0.0)
With serious vaccine-related* AEs	**0 (0.0)**	**1 (0.2)**	**1 (0.2)**
Discontinued** due to a serious vaccine-related AE	0 (0.0)	1 (0.2)	0 (0.0)
Vaccine-related deaths	0 (0.0)	0 (0.0)	0 (0.0)

**Determined by the investigator to be related to the vaccine **Study medication withdrawn*

Protocol 002: Conclusions

Immunogenicity

- Non-inferior immunogenicity in adolescent girls and boys vs. young women for all 9 vaccine HPV types
  - Supports bridging of efficacy findings in young women, 16 to 26 years of age, to girls and boys, 9 to 15 years of age
- Immunogenicity comparable in boys vs. girls

Safety

- Generally well tolerated in all 3 demographic groups

Protocol 009 (qHPV-to-9vHPV Immunobridging): Objectives

Immunogenicity

- To compare anti-HPV 6, 11, 16 and 18 GMTs in adolescent girls who received qHPV vaccine vs. adolescent girls who received 9vHPV vaccine

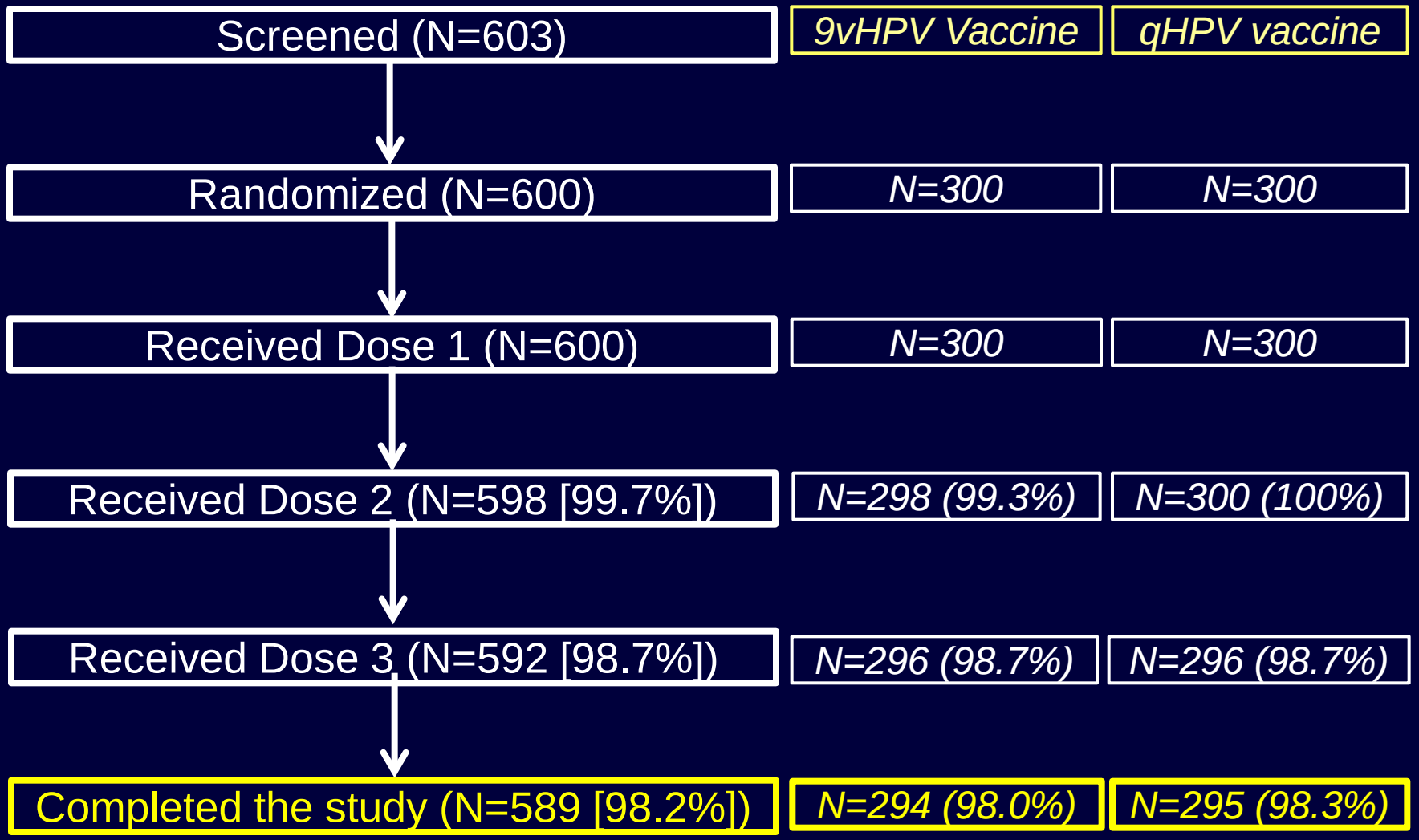
Safety

- To evaluate the safety/tolerability of the qHPV and 9vHPV vaccines in adolescent girls

Protocol 009: Study Design

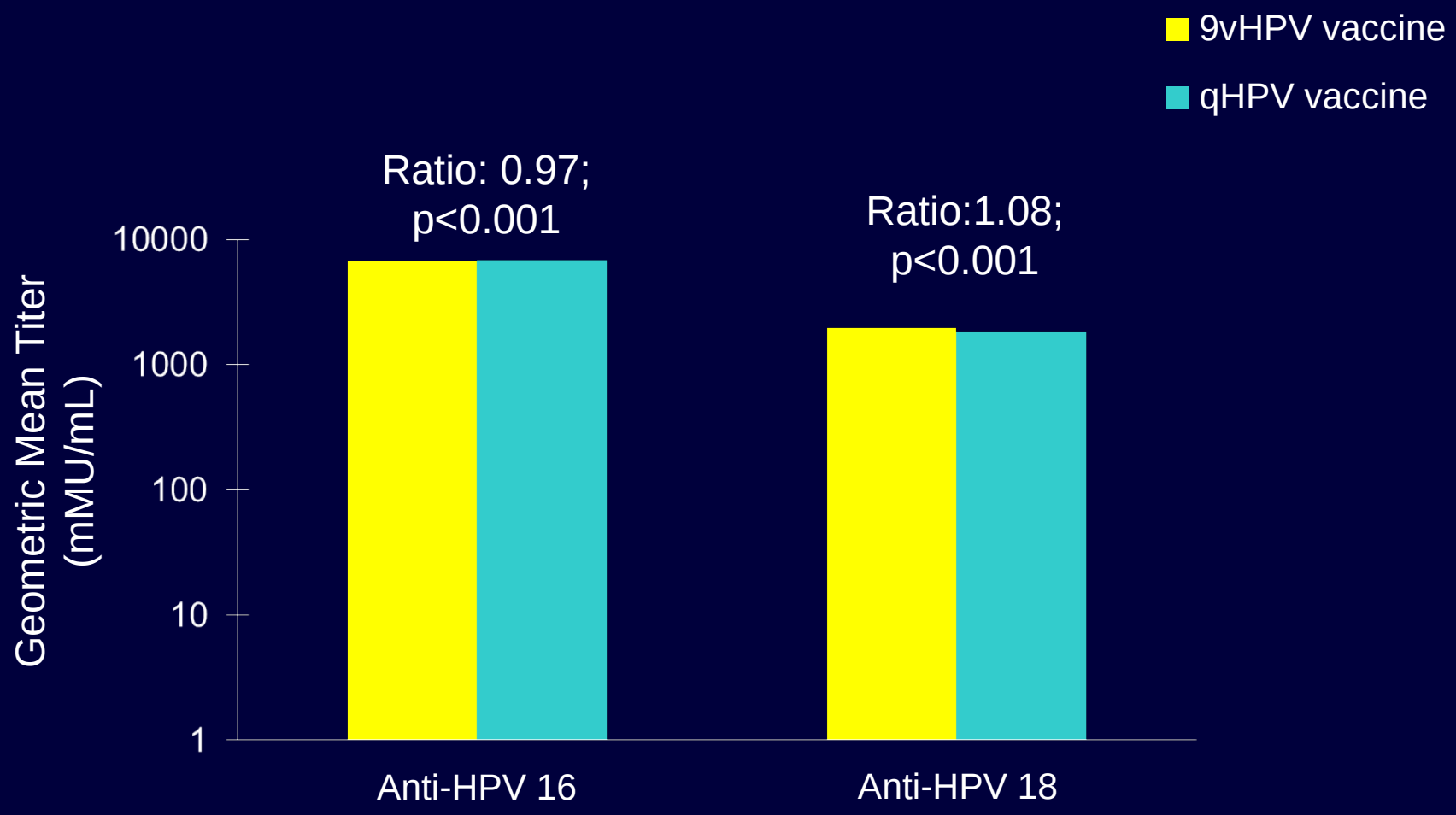
Study Population	**600 girls (9-12 years: ~300; 13-15 years: ~300)** **Equally randomized to 9vHPV vaccine or qHPV vaccine**
Vaccination	**Day 1, Month 2, and Month 6** **Double-blinded study: Subjects receive 9vHPV or qHPV vaccine**
Key Endpoints	**Immunogenicity: *Day 1 and Month 7*** **Anti-HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 titers** **Safety: *Day 1 through Month 7*** **Vaccination Report Card (VRC)-aided surveillance** **Serious Adverse Experiences (SAEs)**

Protocol 009: Subject Disposition

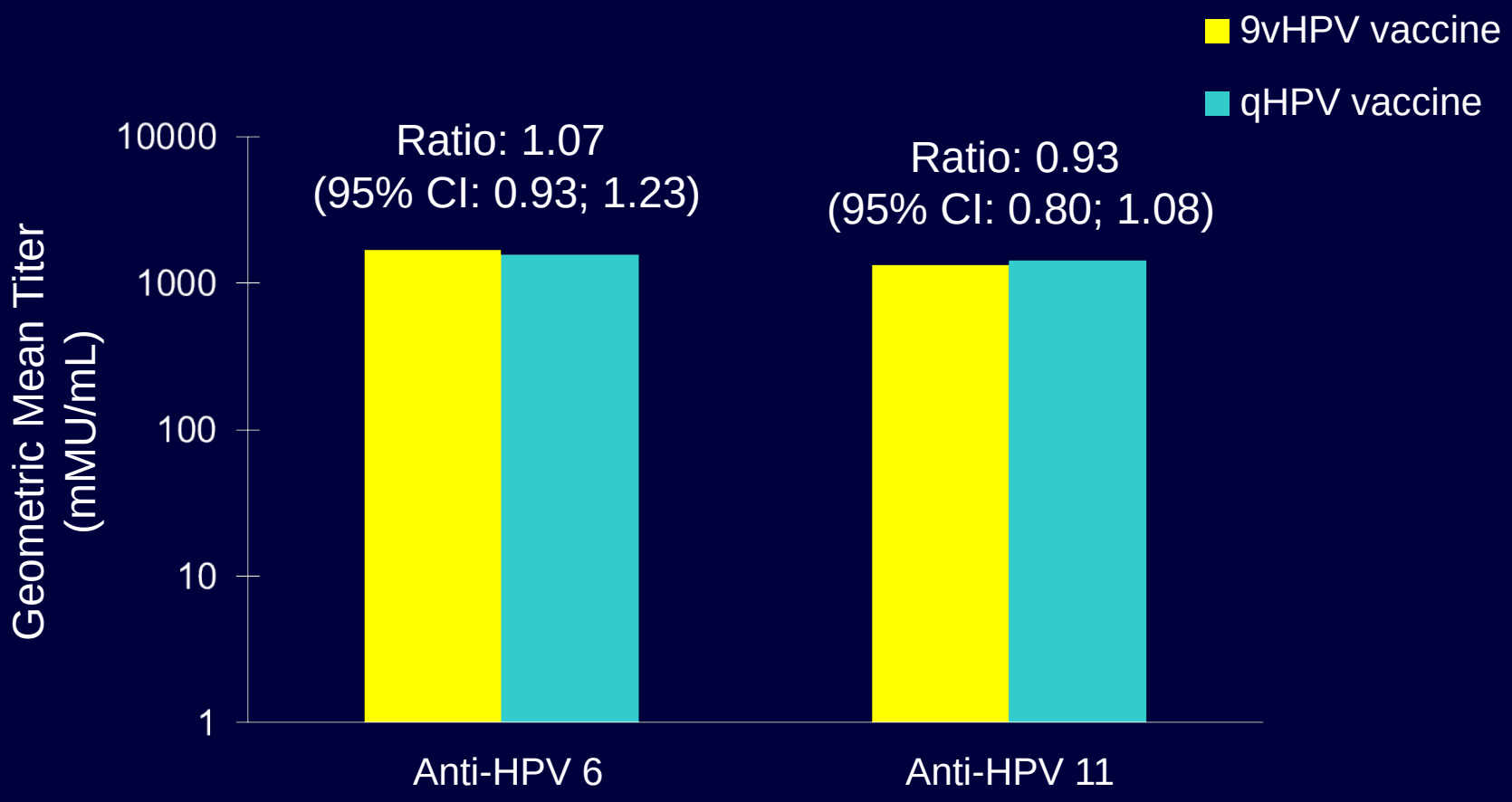


Protocol 009: Non-inferiority of Month 7 cLIA GMT in Girls Administered 9vHPV Vaccine vs. Girls Administered qHPV Vaccine

The non-inferiority criterion was met for both HPV types



Protocol 009: Comparison of Month 7 cLIA GMT in Girls Administered 9vHPV Vaccine vs. Girls Administered qHPV Vaccine



Protocol 009: Month 7 cLIA Seroconversion Rates in Girls Administered 9vHPV Vaccine vs. Girls Administered qHPV Vaccine

	9vHPV Vaccine (N=300)			qHPV Vaccine (N=300)		
Assay	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Anti-HPV 6	273	**100**	98.7; 100	261	**100**	98.6; 100
Anti-HPV 11	273	**100**	98.7; 100	261	**100**	98.6; 100
Anti-HPV 16	276	**100**	98.7; 100	270	**100**	98.6; 100
Anti-HPV 18	276	**100**	98.7; 100	269	**100**	98.6; 100

Protocol 009: Conclusions

Immunogenicity

- Comparable anti-HPV 6/11/16/18 GMTs in adolescent girls who received 9vHPV vaccine vs. adolescent girls who received qHPV vaccine
  - *Supports bridging of efficacy findings with qHPV vaccine to 9vHPV vaccine*

Safety

- Safety profile comparable between 9vHPV vaccine and qHPV vaccine
- Most injection-site reactions were of mild or moderate intensity

Overall Conclusions

- **Successful clinical development program**
  - All efficacy and immunogenicity objectives met
    - Non-inferior anti-HPV 6, 11, 16, 18 responses vs. qHPV vaccine
    - ~97% protection against HPV 31, 33, 45, 52, 58-related disease
    - Non-inferior immunogenicity in adolescents vs. adults
  - Generally well tolerated
    - >10,000 subjects in protocols 001, 002, 009
    - AE profile similar to that of qHPV vaccine
- **Additional data to be presented at future meetings**
  - Concomitant use
  - Prior qHPV vaccine recipients
  - Young men, 16 to 26 years of age
- **Current status**
  - Investigational product currently under FDA review