9-valent HPV (9vHPV) Vaccine Program
Key Results – Part II

ACIP – 25-Jun-2014

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Abbreviations

Abbreviation	Definition
Vaccines	
• 9vHPV vaccine	Investigational 9-valent HPV vaccine
• qHPV vaccine	Licensed quadrivalent HPV vaccine (Gardasil)
Immunological assay	
• HPV-9 cLIA (or cLIA)	HPV 6/11/16/18/31/33/45/52/58 competitive Luminex immunoassay
Pertussis antigens	
• FHA	Filamentous hemagglutinin
• FIM	Fimbrial agglutinogens
• PRN	Pertactin
• PT	Pertussis toxin

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

STUDY RESULTS PRESENTED TO ACIP ON 27-FEB-2014

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	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 TODAY

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 (A, C, Y, W-135); **Tdap vaccine; ***Tdap/polio vaccine*

Ongoing Phase III Studies

Study	Population	N	Objective	Status
Immunobridging study in young men				
003	16-26 yo men and women	2500	Women-to-men immunobridging	Ongoing
Two-dose regimen				
010	9-14 yo boys & girls and 16-26 yo women	1500	Adult (3-dose)-to-adolescent (2-dose) immunobridging	Ongoing

Overall Conclusions: Protocols 001, 002, & 009

SUMMARY OF RESULTS PRESENTED TO ACIP ON 27-FEB-2014

- **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 boys and girls vs. young women
- **Generally well tolerated**
  - >10,000 subjects in protocols 001, 002, 009
  - AE profile similar to that of qHPV vaccine
    - More injection-site adverse events (mostly mild/moderate in intensity)

Presentation Topics

- Concomitant use with other vaccines used in adolescents (girls/boys, 11-15 years of age)
  - **Protocol 005** (Menactra/Adacel)
    - Immunogenicity and safety
  - **Protocol 007** (Repevax)
    - Overall summary
- Evaluation in prior Gardasil recipients (girls/women, 12-26 years of age)
  - **Protocol 006**
    - Safety and immunogenicity
- Integrated summary of safety
  - **All 9vHPV vaccine recipients (>13,000 subjects)**
    - Protocols 001, 002, 005, 006, 007, and 009

PROTOCOLS 005 & 007

CONCOMITANT USE STUDIES

Protocol 005 (Concomitant Use: Menactra/Adacel): Objectives

Immunogenicity

- To demonstrate that concomitant administration of 9vHPV vaccine and Menactra/Adacel does not interfere with the antibody response to any of the vaccine antigens

Safety

- To evaluate the safety/tolerability of the 9vHPV vaccine concomitantly administered with Menactra and Adacel

Menactra: Meningococcal vaccine (A, C, Y, W-135); Adacel: Tdap vaccine

Protocol 005: Study Design

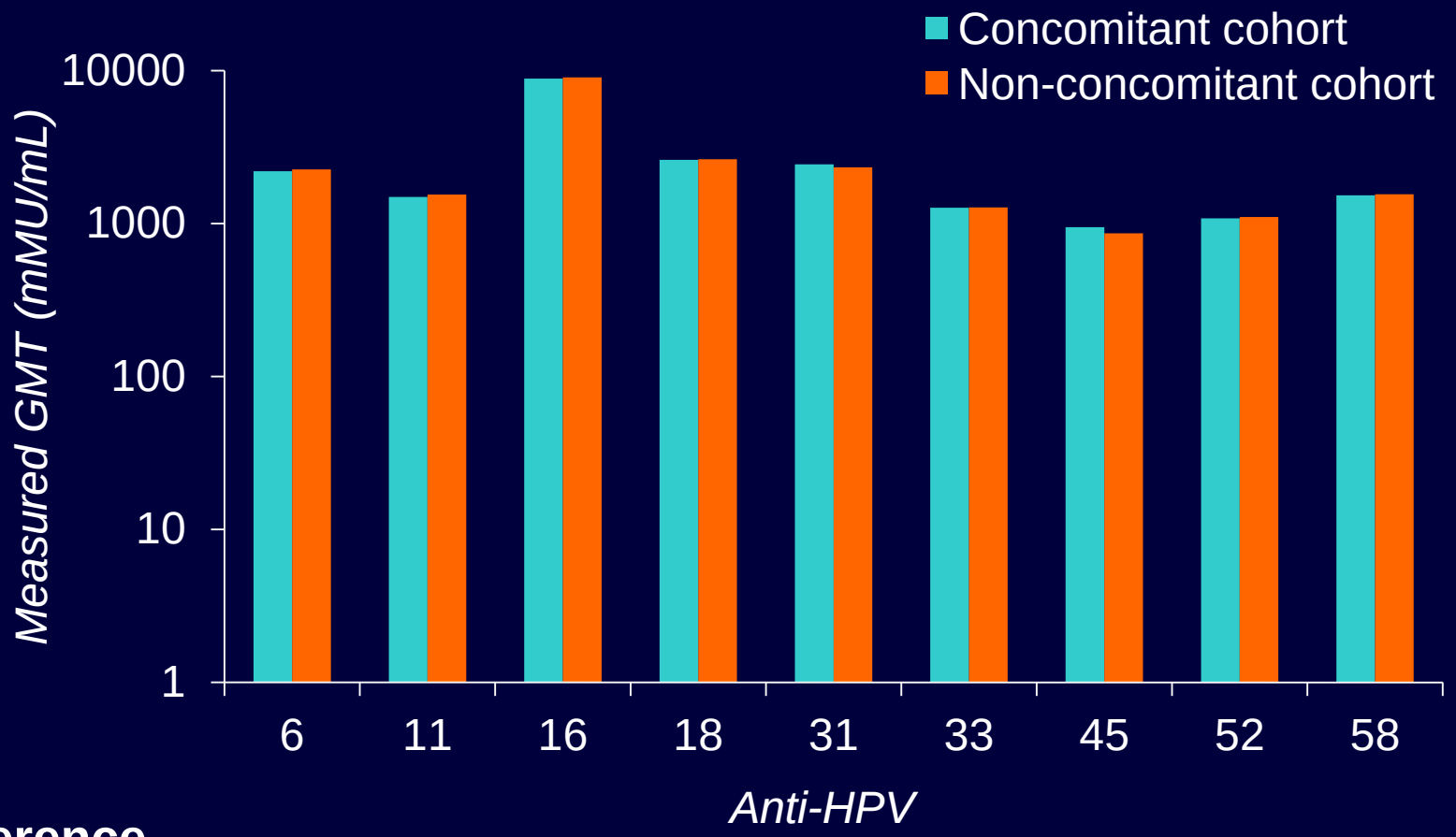
Concomitant Use With Menactra and Adacel

Group	Activity	Study visits				
		Day 1	Month 1	Month 2	Month 6	Month 7
Concomitant group ***520 subjects*** *(260 girls, 260 boys, 11-15 years)*	Vaccination	*9vHPV Menactra Adacel*		*9vHPV*	*9vHPV*	
	Serology testing	*X*	*X*			*X*
Non-concomitant group ***520 subjects*** *(260 girls, 260 boys, 11-15 years)*	Vaccination	*9vHPV*	*Menactra Adacel*	*9vHPV*	*9vHPV*	
	Serology testing	*X*	*X*	*X*		*X*

Menactra: meningococcal vaccine (A, C, Y, W-135); Adacel: Tdap vaccine

Protocol 005: Month 7 HPV-9 cLIA GMT in Concomitant Group vs. Non-concomitant Group After Vaccination with 9vHPV Vaccine

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



Fold difference (ConC/NonconC):	**0.97**	**0.97**	**0.98**	**0.99**	**1.04**	**0.99**	**1.10**	**0.98**	**0.99**

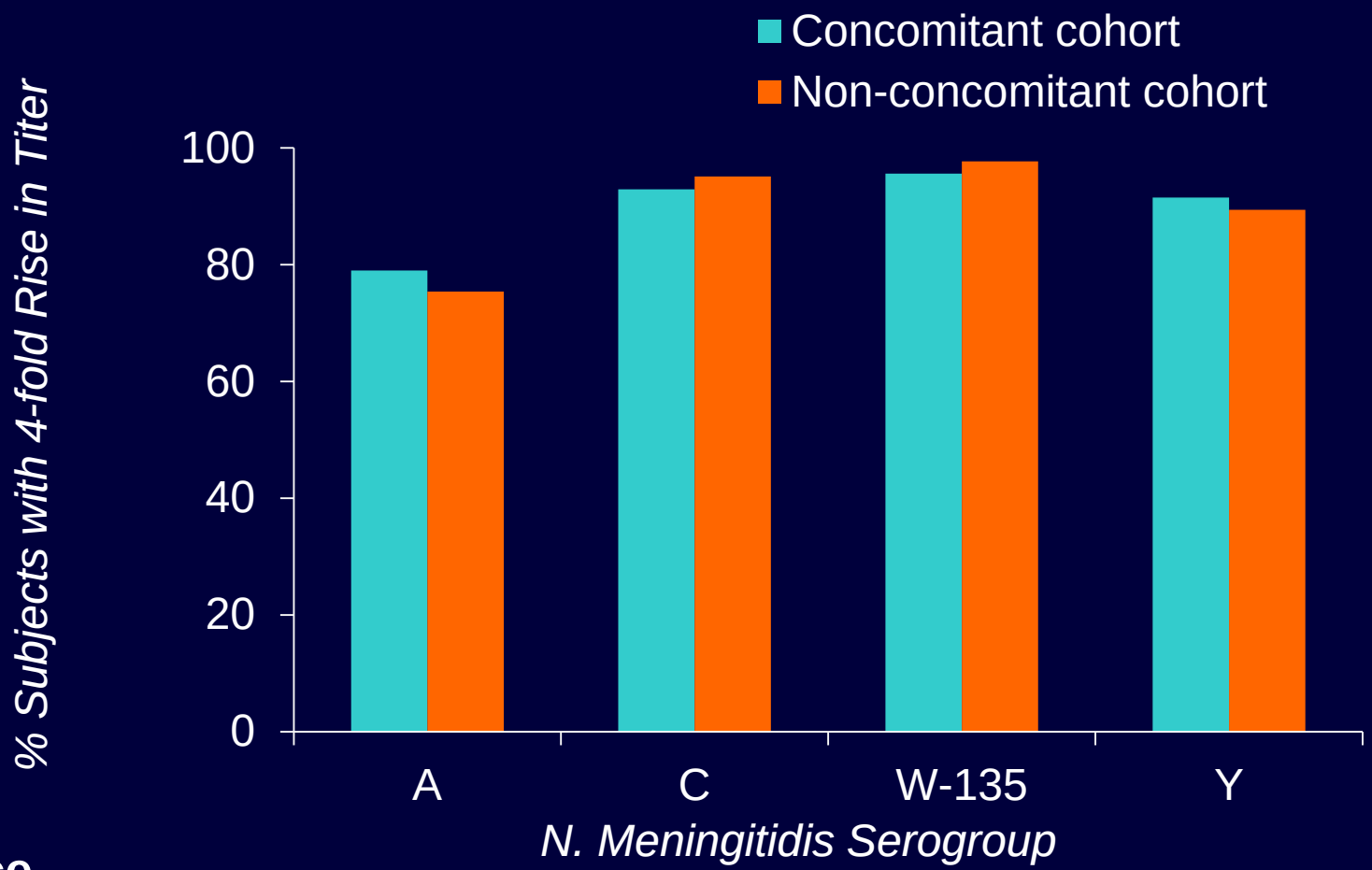
Protocol 005: Month 7 HPV-9 cLIA Seroconversion Rates in Concomitant Group vs. Non-concomitant Group After Vaccination with 9vHPV Vaccine

Assay	9vHPV Vaccine			
	Concomitant Group (N = 619)		Nonconcomitant Group (N = 618)	
	n	Seroconversion (%)	n	Seroconversion (%)
HPV 6	501	**100**	514	**100**
HPV 11	502	**100**	514	**100**
HPV 16	513	**100**	530	**100**
HPV 18	516	**100**	535	**100**
HPV 31	514	**100**	536	**100**
HPV 33	520	**100**	537	**100**
HPV 45	523	**100**	539	**100**
HPV 52	521	**100**	538	**100**
HPV 58	519	**100**	537	**100**

n = number of subjects contributing to the analysis

Protocol 005: Non-Inferiority of % of subjects with 4-fold Rise in Titers for *Neisseria meningitidis* in Concomitant vs. Non-Concomitant Group

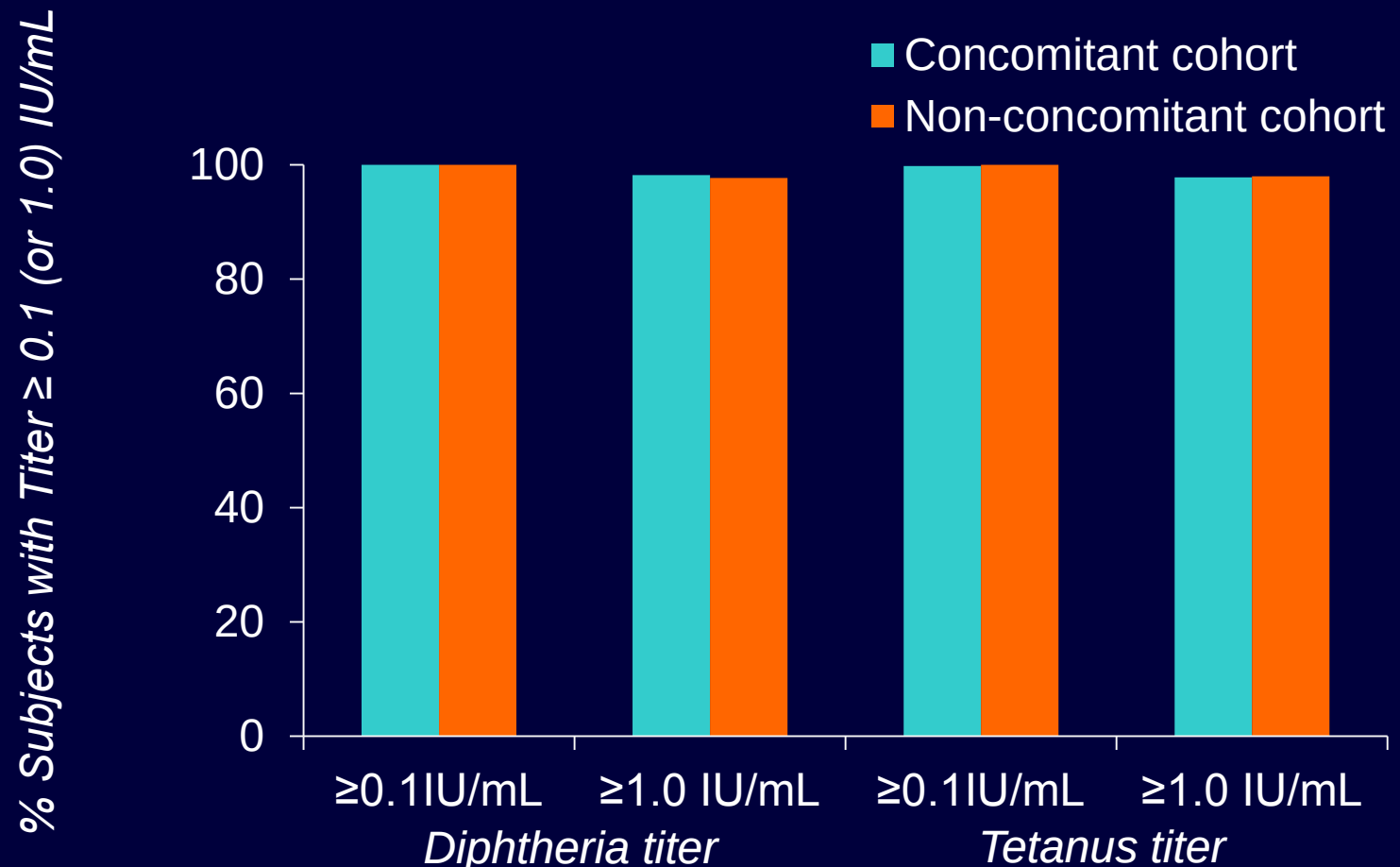
The non-inferiority criterion was met for all 4 *N. meningitidis* serogroups (all p<0.001)



Difference (ConC/NonconC):	**3.8**	**-2.1**	**-2.1**	**2.1**

Protocol 005: Non-inferiority of % Sero(+) for Diphtheria and Tetanus in the Concomitant vs. Non-Concomitant Group

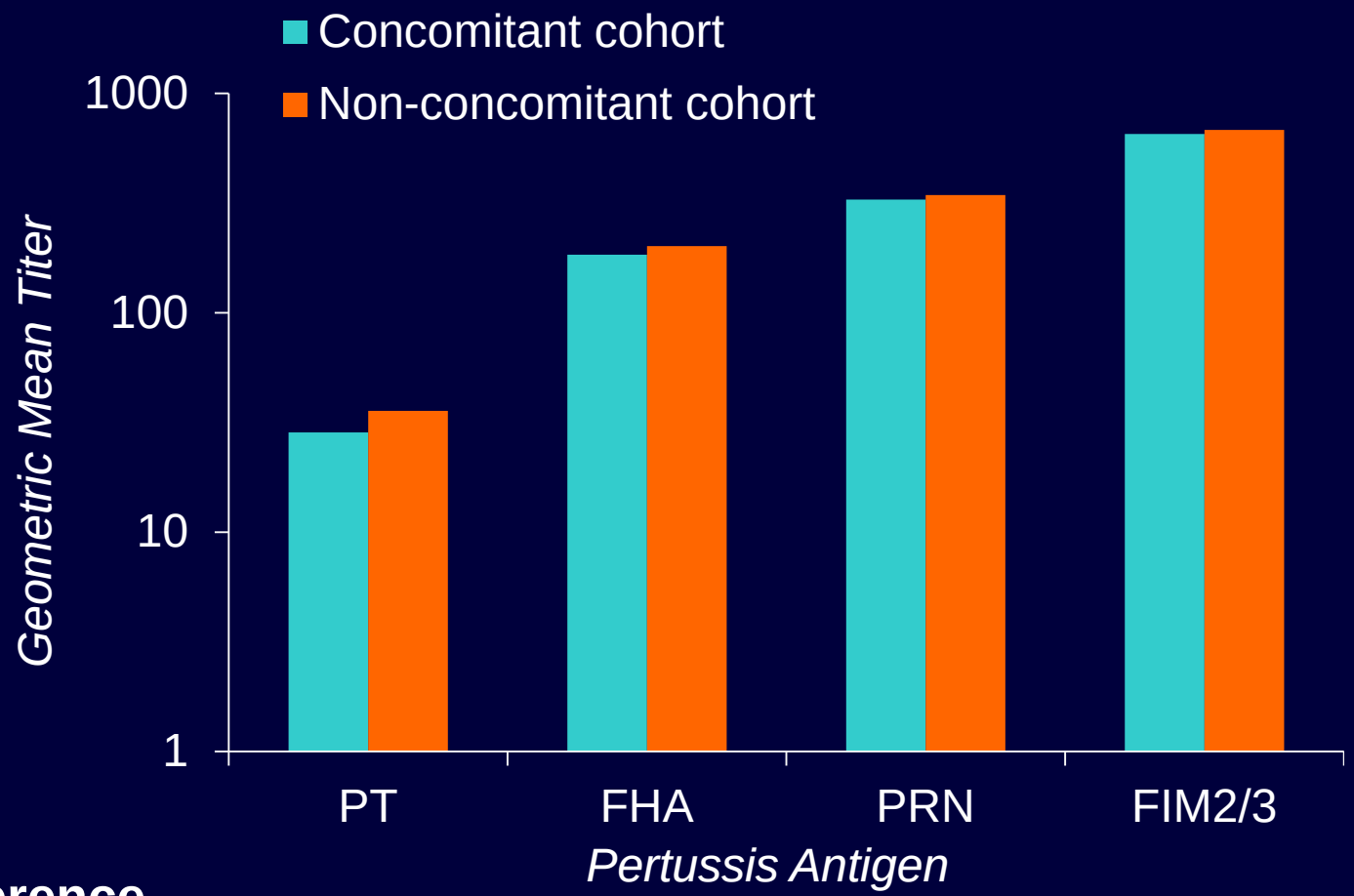
The non-inferiority criterion was met for both diphtheria and tetanus (p<0.001)



Difference (ConC/NonconC):	**0.0**	**0.5**	**-0.2**	**-0.2**

Protocol 005: Non-inferiority of GMT for Pertussis in the Concomitant vs. Non-Concomitant Group

The non-inferiority criterion was met for all 4 pertussis antigens (PT p=0.003; all others p<0.001)



Fold difference (ConC/NonconC):	**0.80**	**0.91**	**0.95**	**0.96**

Protocol 005: Conclusions

9vHPV vaccine can be administered concomitantly with Menactra/Adacel

- No interference with the antibody response to any of the vaccine antigens
- Generally well tolerated

Protocol 007: Overview

Concomitant Use With Repevax (Tdap-IPV vaccine used in Europe)

Summary of the findings

- Concomitant administration of 9vHPV vaccine and Repevax does not interfere with the antibody response to any of the vaccine antigens
- Concomitant administration of 9vHPV vaccine with Repevax is generally well tolerated in young adolescents

PROTOCOL 006

SAFETY / IMMUNOGENICITY IN PRIOR GARDASIL RECIPIENTS

Protocol 006 (Evaluation in Prior Gardasil Recipients): Objectives

Safety

- To evaluate the safety/tolerability of the 9vHPV vaccine in prior Gardasil recipients

Immunogenicity

- To demonstrate that the 9vHPV vaccine is immunogenic with respect to HPV 31, 33, 45, 52, 58 in prior Gardasil recipients

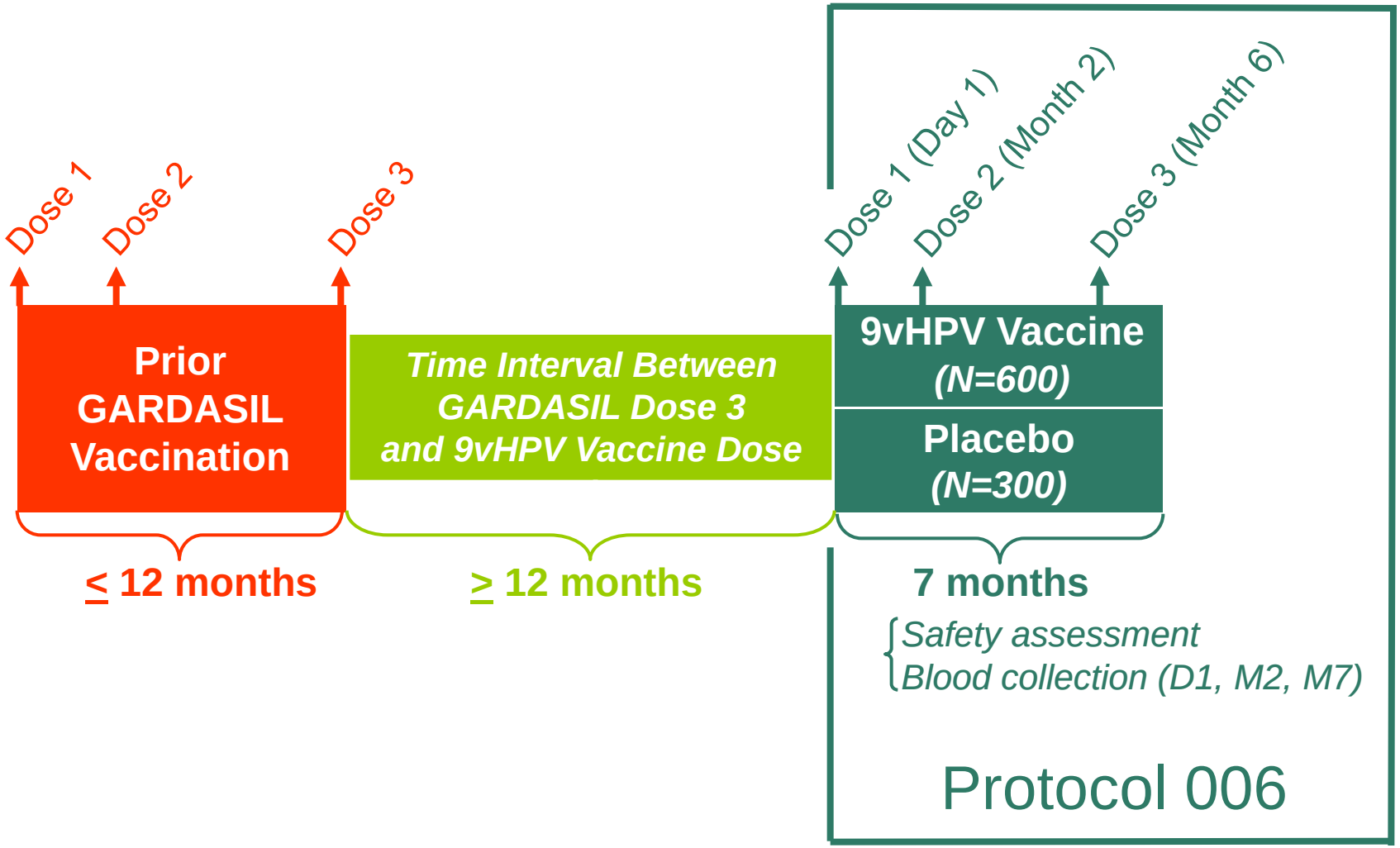
Primarily a safety study to help health care professionals advise their patients about 9vHPV vaccination (e.g., individuals seeking follow-up vaccination or with unknown history of HPV vaccination)

Protocol 006: Study Design

Study Population	**900 girls and young women (12-15 years: ~180; 16-26 years: ~720); all prior Gardasil recipients**
Vaccination	**Day 1, Month 2, and Month 6** **Double-blinded study: Subjects randomized 2:1 to receive 9vHPV vaccine or saline placebo**
Key Endpoints	**Immunogenicity: *Day 1, Month 2, 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 006: Study Design

Use of 9vHPV Vaccine in Prior Gardasil Recipients



AE Summary – Protocol 006
(Females 12 to 26 Years of Age)
(Days 1 to 15 Following Any Vaccination with 9vHPV Vaccine)

Adverse Event	9vHPV Vaccine (N=608)	Saline placebo (N=305)
	n (%)	n (%)
With vaccine-related* AEs	566 (93.1)	174 (57.0)
Injection-site	554 (91.1)	134 (43.9)
Systemic	186 (30.6)	79 (25.9)
Discontinued** due to a vaccine-related AE	3 (0.5)	0 (0.0)
With serious vaccine-related* AEs	1 (0.2)	1 (0.3)
Discontinued** due to a serious vaccine-related AE	0 (0.0)	1 (0.0)
Vaccine-related* deaths	0 (0.0)	0 (0.0)

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

Injection-site AEs (Incidence ≥1%) – Protocol 006
(Females 12 to 26 Years of Age)
(Days 1 to 5 Following Any Vaccination with 9vHPV Vaccine)

Injection-site AE	9vHPV Vaccine (N=608)	Saline placebo (N=305)
	n (%)	n (%)
Pain	549 (90.3)	116 (38.0)
Swelling	298 (49.0)	18 (5.9)
Erythema	257 (42.3)	26 (8.5)
Pruritus	47 (7.7)	4 (1.3)
Hematoma	29 (4.8)	7 (2.3)
Reaction	8 (1.3)	1 (0.3)
Mass	7 (1.2)	2 (0.7)

*Most injection-site AEs were of mild or moderate intensity.

9vHPV Vaccine Immunogenicity in Prior GARDASIL Recipients

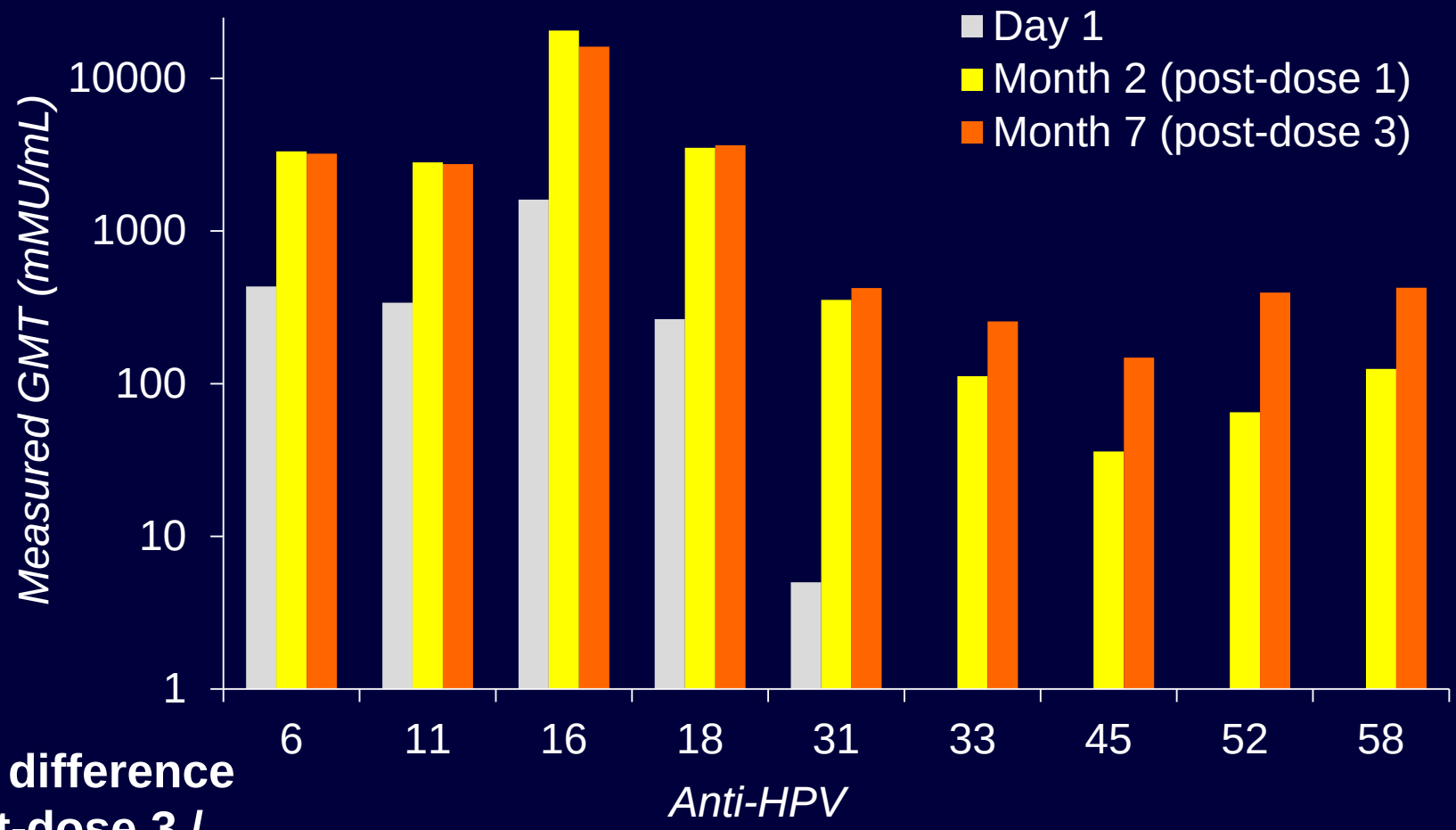
Month 7 cLIA seropositivity rates in girls and young women, 12 to 26 years of age

	9vHPV Vaccine			
	Girls (12-15 yo) (N = 120)		Women (16-26 yo) (N = 495)	
Assay	n	Seropositivity (%)	n	Seropositivity (%)
HPV 6	98	**100**	413	**100**
HPV 11	100	**100**	415	**100**
HPV 16	100	**100**	415	**100**
HPV 18	100	**100**	415	**100**
HPV 31	100	**100**	415	**99.8**
HPV 33	100	**100**	415	**99.8**
HPV 45	100	**99.0**	415	**98.1**
HPV 52	100	**99.0**	415	**99.8**
HPV 58	100	**100**	415	**99.8**

n = number of subjects contributing to the analysis

9vHPV Vaccine Immunogenicity in Prior GARDASIL® Recipients Following Dose 1 and Dose 3

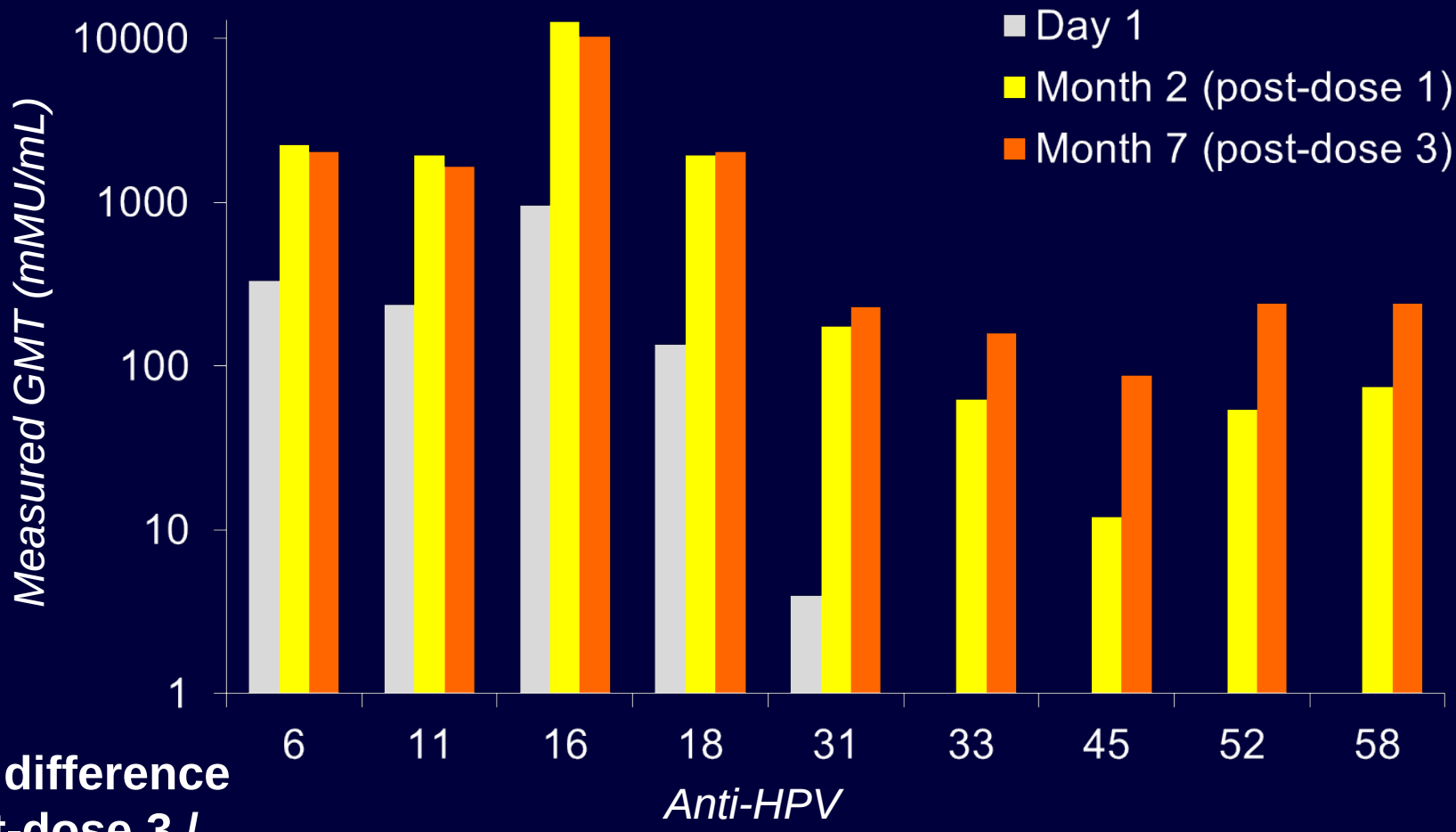
Month 2 & Month 7 cLIA GMT in girls, 12 to 15 years of age



Fold difference (post-dose 3 / post-dose 1):	**0.96**	**0.98**	**0.78**	**1.04**	**1.19**	**2.29**	**4.11**	**6.08**	**3.40**

9vHPV Vaccine Immunogenicity in Prior GARDASIL® Recipients Following Dose 1 and Dose 3

Month 2 & Month 7 cLIA GMT in young women, 16 to 26 years of age



Fold difference (post-dose 3 / post-dose 1):	**0.90**	**0.86**	**0.81**	**1.05**	**1.31**	**2.54**	**7.33**	**4.44**	**3.23**

Protocol 006 – Key Findings

- 9vHPV vaccine has an acceptable safety profile in prior GARDASIL® recipients
  - Most injection-site reactions are of mild or moderate intensity
- 9vHPV vaccine is highly immunogenic with respect to the new types in prior GARDASIL® recipients
  - >98% subjects became seropositive after 3 doses of 9vHPV vaccine

Important considerations

1) The study investigated subjects who received 3 doses of GARDASIL® followed with 3 doses of 9vHPV vaccine

- The study did not investigate mixed regimens of the 2 vaccines

2) This was primarily a safety, placebo-controlled study

- No subjects naïve to HPV vaccination were enrolled in this study

Exploratory Immunogenicity Analysis: Protocol 006 vs. Other 9vHPV Vaccine Studies

- Goal
  - Assess immunogenicity of 9vHPV vaccine after qHPV vaccine vs. 9vHPV vaccine alone
- Caveats
  - Cross-study comparison
    - No subjects received 9vHPV vaccine only in this study
  - Previous antigenic encounter may lower subsequent response to a related antigen (‘Original Antigenic Sin’)
    - Memory response favored over primary response
    - Strong L1 homology among HPV types (example HPV 16 vs. HPV 31: 83% homology)

Cross-Study Immunogenicity Comparison: 9vHPV Vaccine Immunogenicity in Prior GARDASIL® Recipients vs. Subjects Naïve to HPV Vaccination

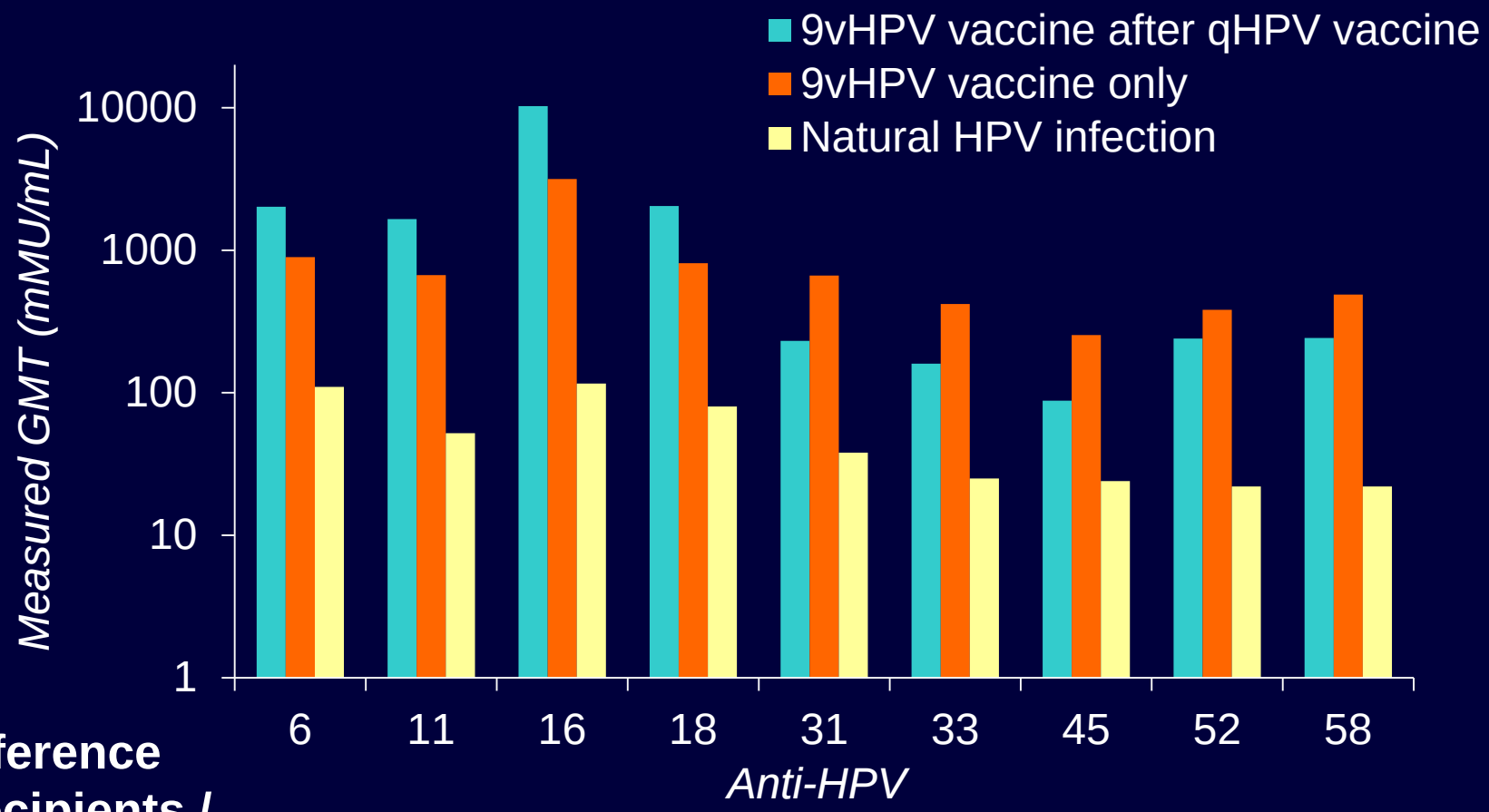
Month 7 cLIA seropositivity rates in young women, 16 to 26 years of age

	9vHPV Vaccine			
	9vHPV Vaccine After qHPV Vaccine (N = 495)		9vHPV Vaccine Only (N = 7260)	
Assay	n	Seropositivity (%)	n	Seropositivity (%)
HPV 6	413	**100**	4321	**99.8**
HPV 11	415	**100**	4327	**100**
HPV 16	415	**100**	4361	**100**
HPV 18	415	**100**	4884	**99.8**
HPV 31	415	**99.8**	4806	**99.8**
HPV 33	415	**99.8**	5056	**99.7**
HPV 45	415	**98.1**	5160	**99.6**
HPV 52	415	**99.8**	4792	**99.8**
HPV 58	415	**99.8**	4818	**99.8**

n = number of subjects contributing to the analysis

Cross-Study Immunogenicity Comparison: 9vHPV Vaccine Immunogenicity in Prior GARDASIL® Recipients vs. Subjects Naïve to HPV Vaccination

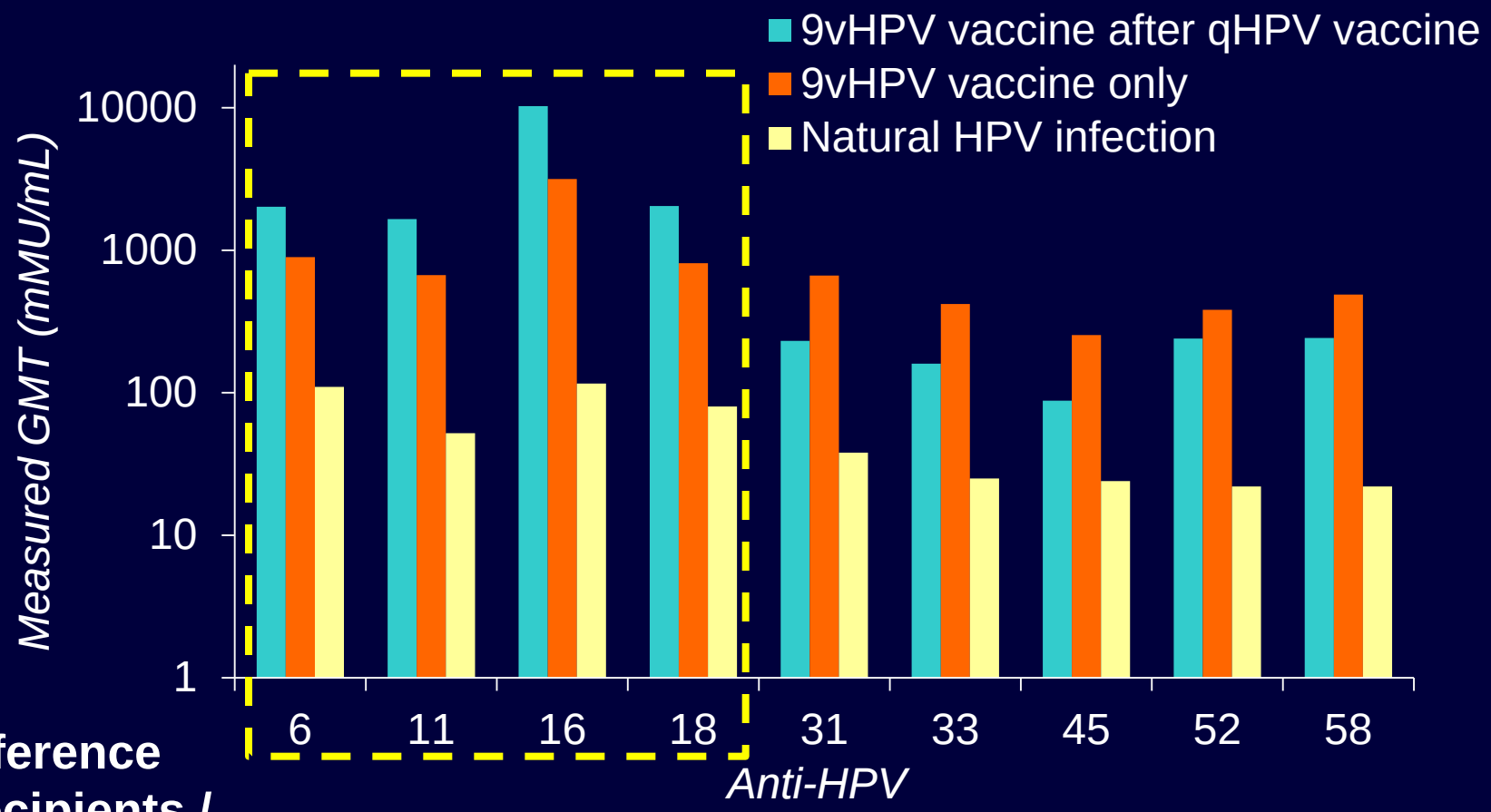
Month 7 cLIA GMT in young women, 16 to 26 years of age



Fold difference (Prior recipients / Naïve to vaccine):	**2.3**	**2.5**	**3.2**	**2.5**	**0.3**	**0.4**	**0.3**	**0.6**	**0.5**

Cross-Study Immunogenicity Comparison: 9vHPV Vaccine Immunogenicity in Prior GARDASIL® Recipients vs. Subjects Naïve to HPV Vaccination

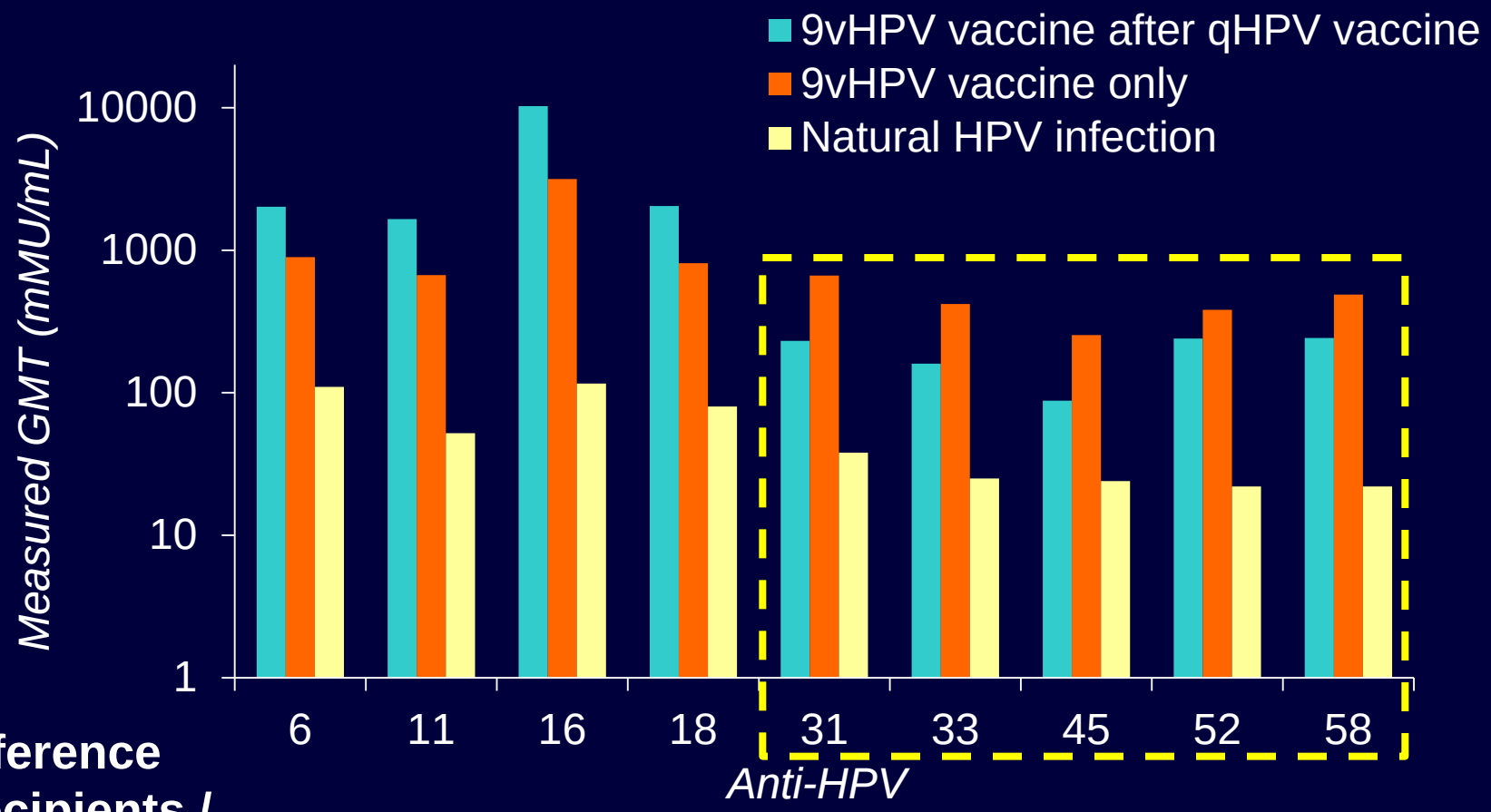
Month 7 cLIA GMT in young women, 16 to 26 years of age



Fold difference (Prior recipients / Naïve to vaccine):	**2.3**	**2.5**	**3.2**	**2.5**	**0.3**	**0.4**	**0.3**	**0.6**	**0.5**

Cross-Study Immunogenicity Comparison: 9vHPV Vaccine Immunogenicity in Prior GARDASIL® Recipients vs. Subjects Naïve to HPV Vaccination

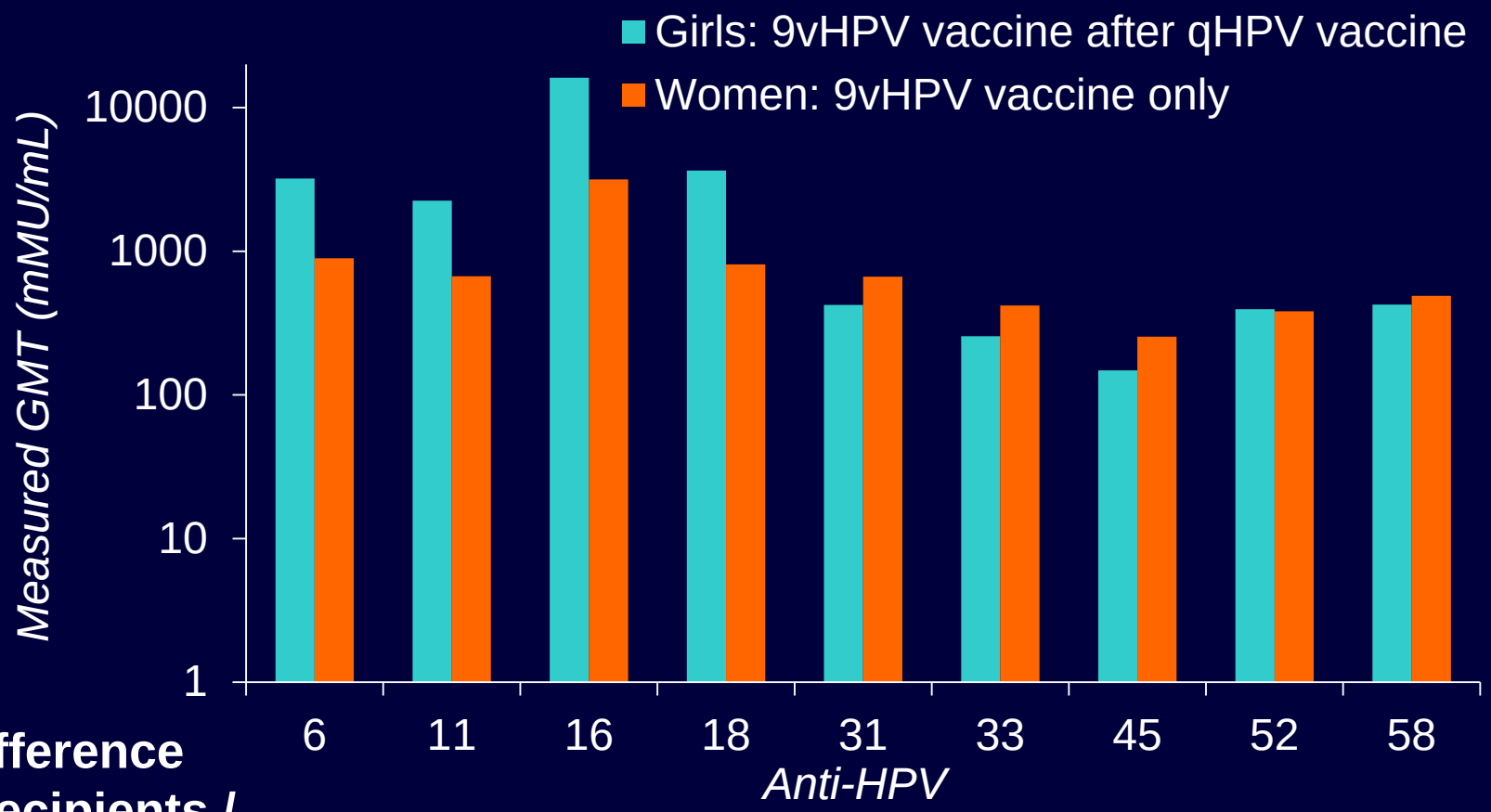
Month 7 cLIA GMT in young women, 16 to 26 years of age



Fold difference (Prior recipients / Naïve to vaccine):	**2.3**	**2.5**	**3.2**	**2.5**	**0.3**	**0.4**	**0.3**	**0.6**	**0.5**

Cross-Study Immunogenicity Comparison: 9vHPV Vaccine Immunogenicity in Prior GARDASIL® Recipients vs. Subjects Naïve to HPV Vaccination

Month 7 cLIA GMT in girls (prior Gardasil recipients), 12 to 15 years of age vs. young women (naïve to HPV vaccination) 16 to 26 years of age



Fold difference (Prior recipients / Naïve to vaccine):	**3.6**	**3.4**	**5.1**	**4.5**	**0.6**	**0.6**	**0.6**	**1.0**	**0.9**

Results of the Cross-Study Immunogenicity Comparison

- Results should be ***interpreted with caution*** (exploratory analysis comparing across different studies)
  - Consistent with previous observations of lower response to antigenic variants following initial exposure to a given antigen
- Practical consequences of these findings: likely limited
  - Seroconversion rates are high in all subjects
  - Clinical significance of differences in GMTs between vaccination groups is unknown (no known threshold of antibody protection)
  - In Protocol 001, lower Month 7 anti-HPV 31, 33, 45, 52, and 58 titers are not correlated with lower efficacy
  - Impact of 'Original Antigenic Sin' considered limited in the context of influenza vaccination
    - Revaccination is associated with reduced mortality risk compared with first time vaccination *(Voordouw AC., JAMA 292:2089-95, 2004)*

INTEGRATED SAFETY DATA

PROTOCOLS 001, 002, 005, 006, 007, 009

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

(Days 1 to 15 Following Any Vaccination)

Adverse Events	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)
Vaccine-related* deaths	0 (0.0)	0 (0.0)

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

Vaccine-Related AE Summary (Protocols 001, 002, 005, 006, 007, 009)

(Days 1 to 15 Following Any Vaccination with 9vHPV Vaccine)

Adverse Event	Subjects Who Received 9vHPV Vaccine (N=13,307)
	n (%)
Vaccine-related* AEs	11,956 (89.8)
Injection-site	11,750 (88.3)
Systemic	3,736 (28.1)
Discontinued** due to a vaccine-related AE	11 (0.1)
Serious vaccine-related* AEs	5 (0.0)
Discontinued** due to a serious vaccine-related AE	2 (0.0)
Vaccine-related* deaths	0 (0.0)

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

Injection-site AEs (Incidence ≥1%) (Protocols 001, 002, 005, 006, 007, 009)

(Days 1 to 5 Following Any Vaccination with 9vHPV Vaccine)

Injection-site AE	Subjects Who Received 9vHPV Vaccine (N=13,307)
	n (%)
Pain	11,352 (85.3)
Swelling	5,010 (37.6)
Erythema	4,228 (31.8)
Pruritus	585 (4.4)
Hematoma	209 (1.6)
Bruising	139 (1.0)
Hemorrhage	127 (1.0)

Most injection-site AEs were mild to moderate in intensity

Systemic Vaccine-Related* AEs (Incidence ≥1%) (Protocols 001, 002, 005, 006, 007, 009)

(Days 1 to 15 Following Any Vaccination with 9vHPV Vaccine)

Systemic Vaccine-related AE	Subjects Who Received 9vHPV Vaccine (N=13,307)
	n (%)
Headache	1,845 (13.9)
Pyrexia	883 (6.6)
Nausea	457 (3.4)
Dizziness	321 (2.4)
Fatigue	258 (1.9)

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

Vaccine-Related* Serious Adverse Events (Protocols 001, 002, 005, 006, 007, 009)

(Subjects who Received 9vHPV Vaccine)

Relative Day of Onset	Adverse event	Hospitalized	Duration	Outcome	Discontinued Vaccine
1d PD1	Allergy to vaccine	No	23 hours	Resolved	Yes
1d PD1	Asthmatic crisis	Yes	3 days	Resolved	Yes
2d PD1	Tonsillitis	No	5 days	Resolved	No
1d PD3	Headache	Yes	1.57 weeks	Resolved	No
2d PD3	Pyrexia	No	2 days	Resolved	No

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

Safety Conclusions

- Generally well tolerated in >13,000 subjects
  - Few discontinuations
  - Few vaccine-related SAEs
  - No vaccine-related deaths
- Adverse experience profile generally comparable to that of qHPV vaccine
  - More injection-site AEs (most are mild/moderate in intensity)
- Adverse experience profile comparable across
  - Age (9-15 y/o vs. 16-26 y/o)
  - Gender
  - Race (White, Black, Asian, other)
  - Ethnicity (Latino vs. non-Latino)
  - HPV status at baseline

  (data not shown in this presentation due to time consideration)

Overall Summary

- 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 boys and girls vs. young women
- Generally well tolerated; AE profile similar to that of qHPV vaccine
  - More injection-site AEs (most are mild/moderate in intensity)
- Can be co-administered with Menactra and Adacel
- Generally well tolerated and highly immunogenic in prior qHPV vaccine recipients
- Investigational product under review by the FDA