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

ACIP – 30-Oct-2014

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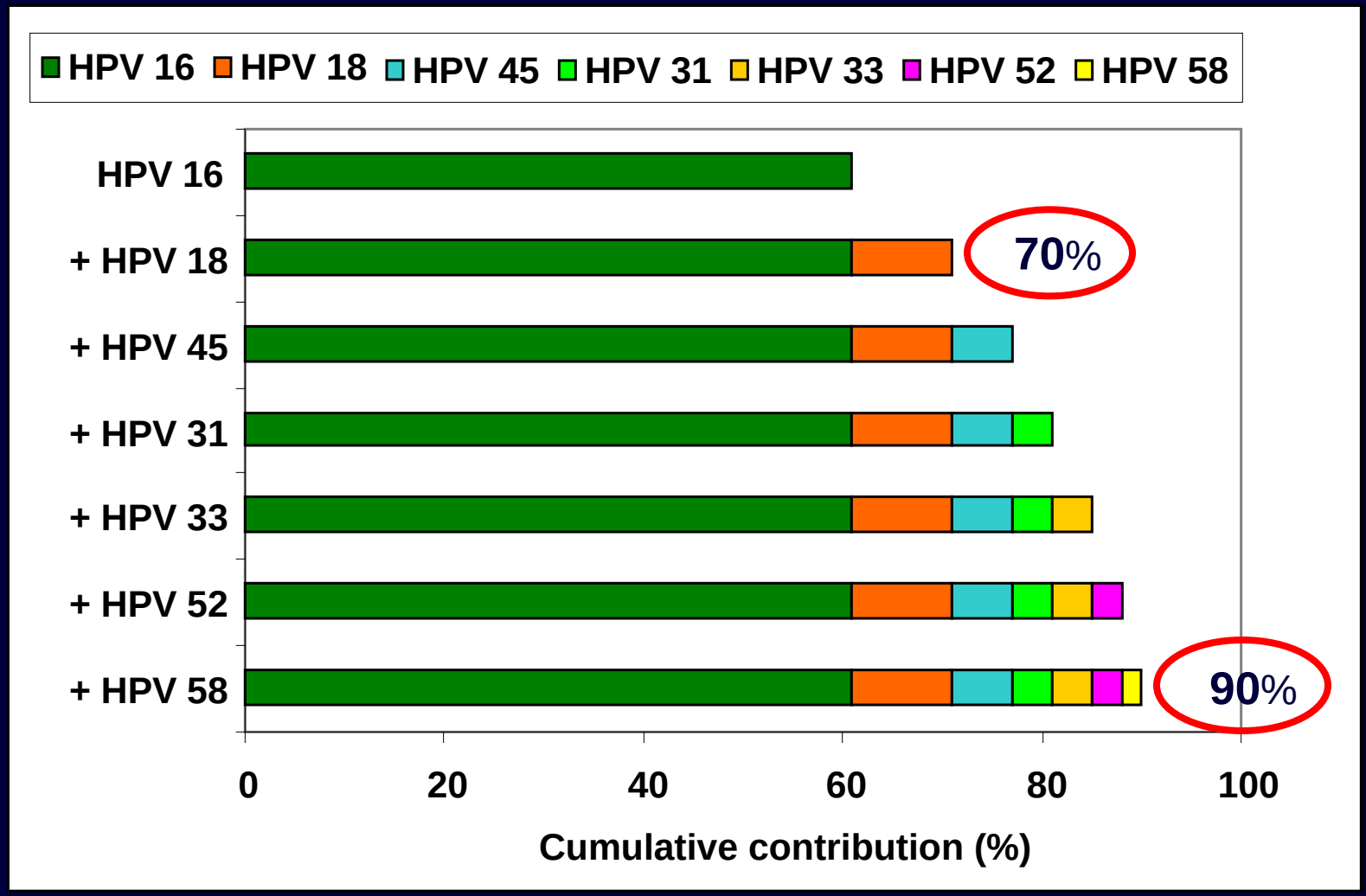
Abbreviations

Abbreviation	Definition
Vaccines	
• 9vHPV vaccine	Investigational 9-valent HPV vaccine
• qHPV vaccine	Licensed quadrivalent HPV vaccine (Gardasil)
Genital Lesions	
• AIS	Adenocarcinoma in situ
• 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*

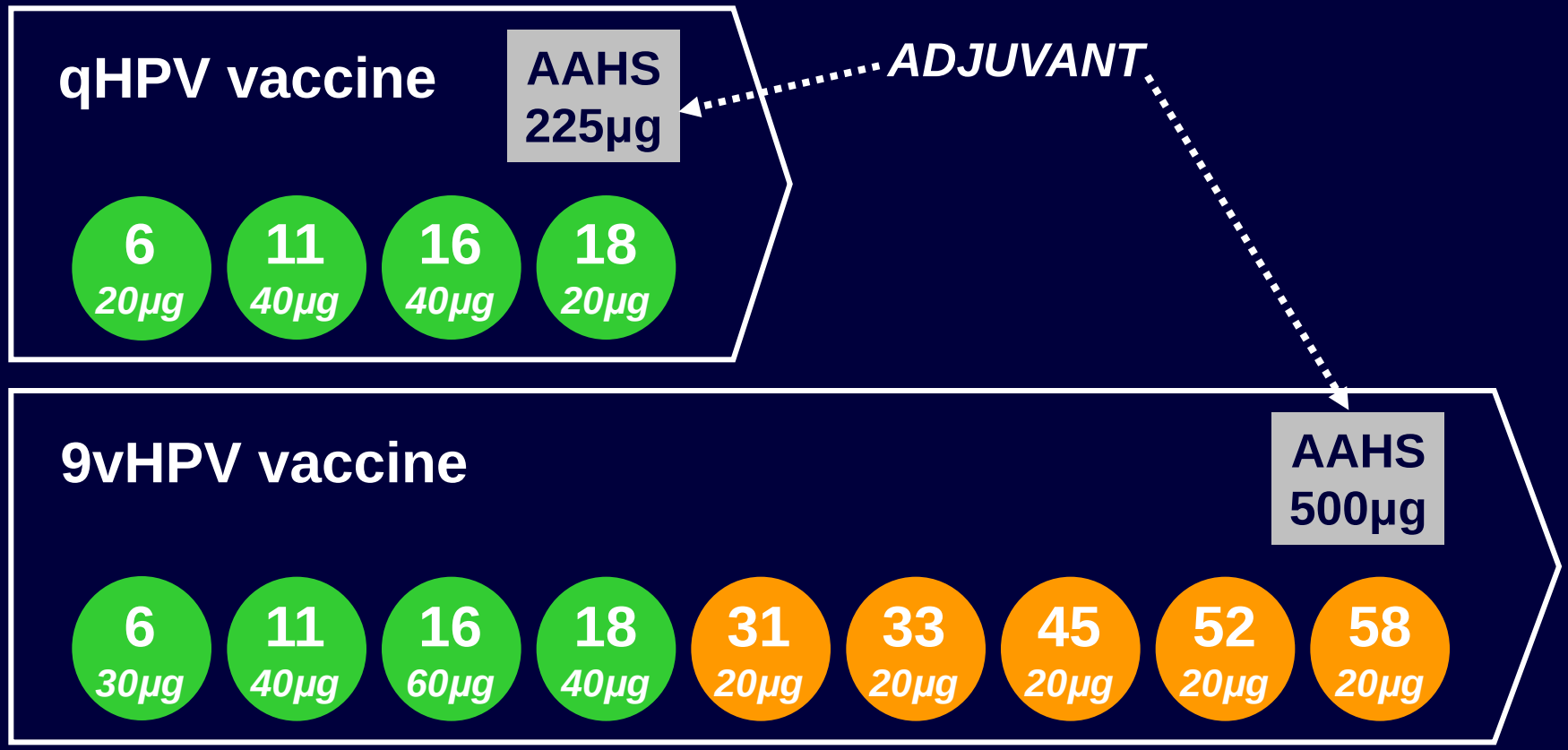
***Estimates based on several meta analyses & results of analyses conducted among all lesions (HPV positive & negative) in placebo cohorts of several GARDASIL® clinical trials*

Relative Contribution of HPV Types in 9vHPV Vaccine to HPV-related Non-cervical Cancers Worldwide

Type of lesion	6/11/16/18 Contribution	31/33/45/52/58 Contribution	Overall 9V Contribution
Vulvar cancer	70-75%	10-15%	85-90%
Vaginal cancer	65%	20%	80-85%
Anal cancer	85-90%	5-10%	90-95%

References: DeSanjose et al Eur J Cancer 2013; Alemany et al Eur J Cancer 2014; Alemany et al. Int J Cancer 2014

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)
Men	Non-inferior immunogenicity in young men 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
Pivotal Studies

STUDY RESULTS PRESENTED 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	Base study completed Extension ongoing*
009	9-15 yo girls	600	qHPV-to-9vHPV immunobridging	Completed

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

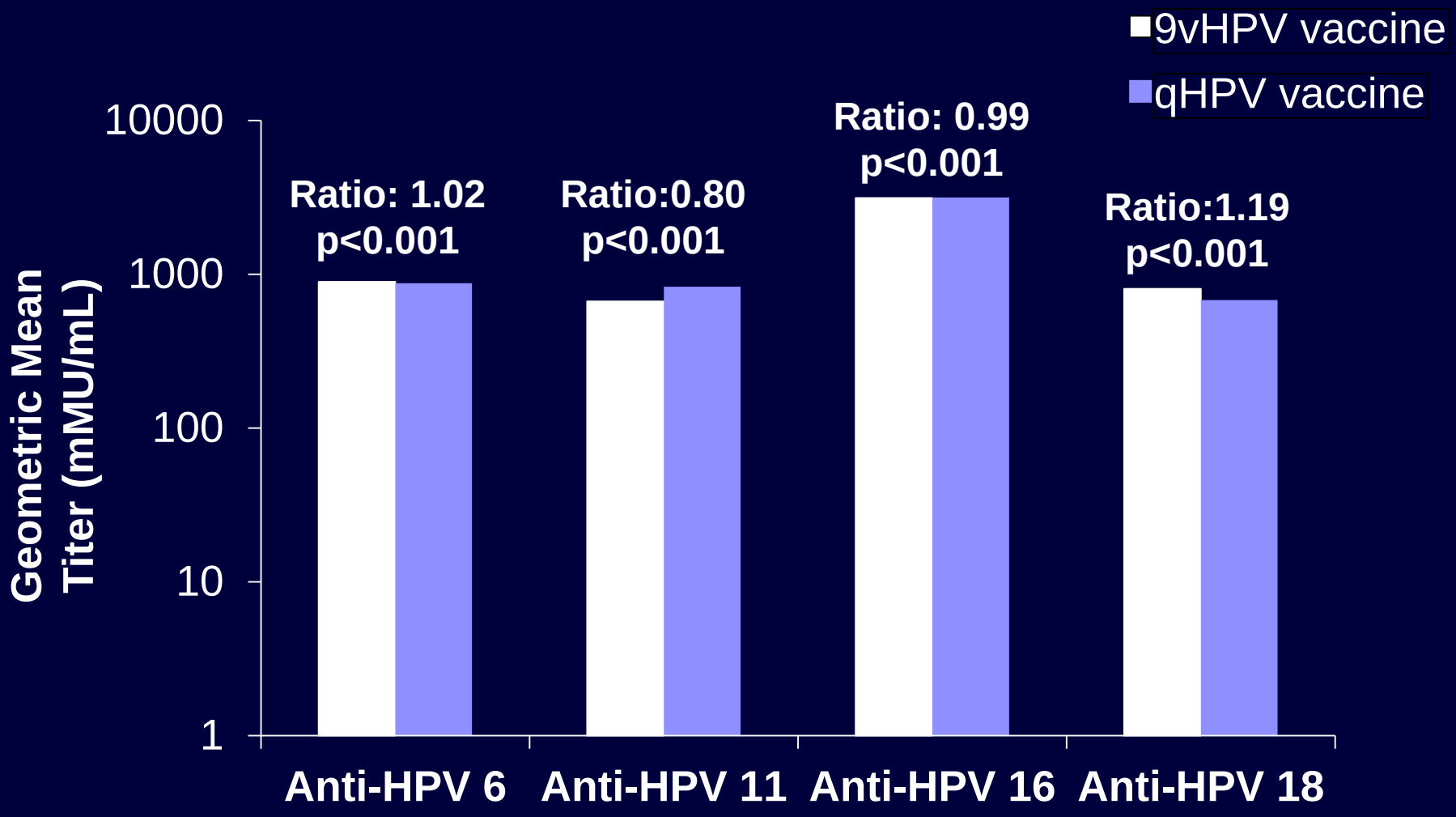
Pivotal Studies: Protocols 001, 002, & 009

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

- **All efficacy and immunogenicity objectives met**
  - Original HPV types (6, 11, 16, 18)
    - Non-inferior anti-HPV 6, 11, 16, 18 response vs. qHPV vaccine
    - Similar protection against disease
  - Additional HPV types (31, 33, 45, 52, 58)
    - ~97% protection against HPV 31, 33, 45, 52, 58-related disease
  - Adolescents
    - 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)

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)



Anti-HPV 6/11/16/18 Disease Endpoints Protocol 001

Supportive Analysis – Per Protocol Efficacy Population

	9vHPV Vaccine (N=7,099)		qHPV Vaccine (N=7,105)	
Endpoint	Cases/n	Rate (95% CI)	Cases/n	Rate (95% CI)
HPV 16/18-related				
CIN 2/3 or AIS	**1** / 5715	0.6 (0.0, 3.3)	**0** / 5732	0.0 (0.0, 2.2)
VIN 2/3	**0** / 5762	0.0 (0.0, 2.0)	**0** / 5789	1.1 (0.0, 2.0)
VaIN 2/3	**0** / 5762	0.0 (0.0, 2.0)	**2** / 5789	1.1 (0.1, 4.0)
HPV 6/11/16/18-related				
CIN (any grade)	**1** / 5823	0.6 (0.0, 3.3)	**3** / 5832	1.8 (0.4, 5.1)
Condyloma	**5** / 5876	2.7 (0.9, 6.3)	**1** / 5893	0.5 (0.0, 3.0)

** Rate is number of cases per 10,000 person-years*

HPV 6/11/16/18 Disease Endpoints Protocol 001 and Gardasil Historical Cohorts

Supportive Analysis – Per Protocol Efficacy Population

	V503-001		V501 historic cohorts*	
Endpoint	9vHPV Cases/n	qHPV Cases/n	qHPV Cases/n	Placebo Cases/n
HPV 16/18-related				
CIN 2/3 or AIS	**1** / 5715	**0** / 5732	**2** / 8493	**112** / 8464
VIN 2/3	**0** / 5762	**0** / 5789	**0** / 7772	**10** / 7744
VaIN 2/3	**0** / 5762	**2** / 5789	**0** / 7772	**9** / 7744
HPV 6/11/16/18-related				
CIN (any grade)	**1** / 5823	**3** / 5832	**9** / 7864	**225** / 7865
Condyloma	**5** / 5876	**1** / 5893	**2** / 7900	**193** / 7902

** Based on the GARDASIL US label*

Protocol 001: Efficacy Against HPV 31/33/45/52/58 [1 of 2]
(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)**

Protocol 001: Efficacy Against HPV 31/33/45/52/58 [2 of 2]
(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)
Vaccine-related* deaths	0 (0.0)	0 (0.0)

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

9vHPV Vaccine Studies – Initial Filing Supportive Studies

RESULTS PRESENTED ON 25-JUN-2014

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*

Supportive Studies: Protocols 005, 006, & 007

SUMMARY OF RESULTS PRESENTED TO ACIP ON 25-JUN-2014

- **All efficacy and immunogenicity objectives met**
  - 9vHPV vaccine can be administered concomitantly with
    - *Menactra* (meningococcal vaccine: A, C, Y, W-135)
    - *Adacel* (Tdap vaccine)
    - *Repevax* (Tdap-IPV vaccine, licensed in the EU)
  - 9vHPV vaccine is highly immunogenic in prior qHPV vaccine recipients
- **Integrated safety (P001, P002, P005, P006, P007)**
  - Generally well tolerated in >13,000 subjects
    - Generally comparable AE profile across age, gender, race, ethnicity
  - AE profile similar to that of qHPV vaccine
    - More injection-site adverse events (mostly mild/moderate in intensity)
  - Generally well tolerated in prior qHPV vaccine recipients

Protocol 003 (Women-Men Immunobridging): Study Design

Study Population	**1,100 young women (16-26 years)** **1,100 heterosexual men (HM) (16-26 years)** **300 men having sex with men (MSM) (16-26 years)**
Vaccination	**3-dose regimen (Day 1, Month 2, and Month 6)** **Open label study: All subjects receive 9vHPV vaccine**
Key Endpoints	**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 Month 12*** **Vaccination Report Card (VRC)-aided surveillance** **Serious Adverse Experiences (SAEs)**

Protocol 003 (Women-Men Immunobridging): Key Objectives

Immunogenicity

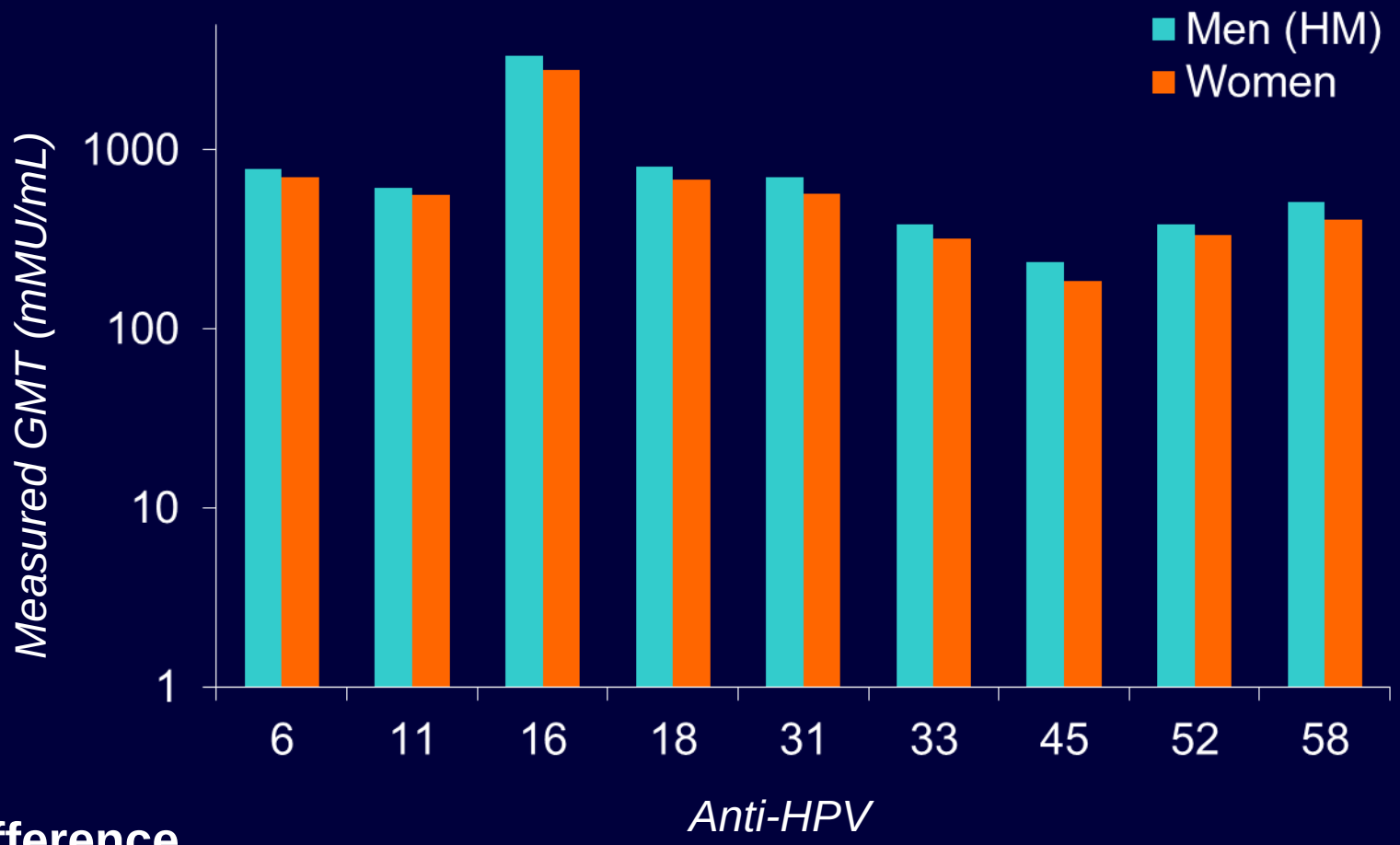
- To demonstrate non-inferior immunogenicity of 9vHPV vaccine in men (HM) 16-26 years of age vs. women 16-26 years of age
- To summarize 9vHPV vaccine immunogenicity in MSM
  - *Rationale: immunogenicity of qHPV vaccine lower in MSM than in HM* (secondary objective; results not included in this presentation)

Safety

- To evaluate the safety/tolerability of the 9vHPV vaccine in young men and young women 16-26 years of age

Protocol 003: Non-inferiority of Month 7 cLIA GMT in Men (HM) vs. Women After Vaccination with 9vHPV Vaccine

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



Fold difference (Men/Women):	1.1	1.1	1.2	1.2	1.2	1.2	1.3	1.2	1.3

Protocol 003: Non-inferiority of Month 7 cLIA Seroconversion in Men (HM) 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			
	Men (HM) (N = 1,103)		Young Women (N = 1,099)	
	n	Seroconversion (%)	n	Seroconversion (%)
HPV 6	847	**99.6**	708	**99.6**
HPV 11	851	**100**	712	**99.9**
HPV 16	899	**100**	781	**99.9**
HPV 18	906	**99.9**	831	**99.8**
HPV 31	908	**100**	826	**100**
HPV 33	901	**100**	853	**99.9**
HPV 45	909	**99.8**	871	**99.5**
HPV 52	907	**100**	849	**99.8**
HPV 58	897	**100**	839	**99.8**

n = number of subjects contributing to the analysis

Protocol 003: Vaccine-Related AE Summary (Day 1 to Month 12)

Subjects	Men N=1,393 n (%)	Women N=1,074 n (%)
All vaccine-related* AEs	**987 (70.9)**	**924 (86.0)**
Injection-site	943 (67.7)	909 (84.6)
Systemic	225 (16.2)	252 (23.5)
Discontinued** due to a vaccine-related AE	2 (0.1)	3 (0.3)
With serious vaccine-related* AEs	**0 (0.0)**	**0 (0.0)**
Discontinued** due to a serious vaccine-related AE	0 (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*

Protocol 003: Conclusions

Immunogenicity

- Non-inferior immunogenicity in young men (HM) vs. young women for all 9 vaccine HPV types
  - Supports bridging of efficacy findings in young women, 16 to 26 years of age, to men 16 to 26 years of age

Safety

- Generally well tolerated in young men and young women
  - Lower frequency of adverse events in young men vs. young women (similar to qHPV vaccine)

Overall Summary of the 9vHPV Vaccine Program

- Original HPV types (6, 11, 16, 18)
  - Non-inferior anti-HPV 6, 11, 16, 18 responses vs. qHPV vaccine
  - Similar protection against disease
- Additional HPV types (31, 33, 45, 52, 58)
  - ~97% protection against HPV 31, 33, 45, 52, 58-related disease
- Non-inferior immunogenicity
  - in boys and girls vs. young women
  - in young men vs. young women
- Generally well tolerated; AE profile similar to that of qHPV vaccine
  - More injection-site AEs (most are mild/moderate in intensity)
  - >15,000 subjects received 9vHPV vaccine
- 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