9-valent HPV (9vHPV) Vaccine Program Safety and Immunogenicity Study in Women 27-45 Years

Advisory Committee on Immunization Practices

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Overview of Information Previously Presented to the ACIP [1 of 2]

- Clinical trials
  - The qHPV vaccine prevents HPV6/11/16/18-related persistent infection and disease in women 27-45 years of age in FUTURE III
    - 95% efficacy against HPV6/11/16/18-related CIN and condyloma in women 27-45 years of age (FUTURE III study)
    - High efficacy consistently observed across the 16-45 year age range in the FUTURE I, II, and III studies
    - Durable protection (~10 years) in women 27-45 years of age in a long-term follow-up extension of the FUTURE III study
  - Regulatory agencies have concluded that qHPV vaccine efficacy and immunogenicity results can be bridged to 9vHPV vaccine
    - Both vaccines contain VLPs for HPV6/11/16/18 and are manufactured using similar processes
    - Consistent success in efficacy and immunogenicity bridging studies of qHPV and 9vHPV vaccines across age and gender

FUTURE I & II: efficacy studies of qHPV vaccine in women 16-26 years of age (NCT00092521; NCT00092534)
FUTURE III: efficacy study of qHPV vaccine in women 24-45 years of age (NCT00090220)

Overview of Information Previously Presented to the ACIP [2 of 2]

- Regulatory
  - Based on clinical trial results, the FDA and other regulatory agencies have granted an indication for the 9vHPV vaccine in adults over 26 years of age
    - In the US, the 9vHPV vaccine age indication was expanded from 9-26 years to 9-45 years in Oct 2018 (following priority review by the FDA) based on qHPV vaccine efficacy data and bridging to 9vHPV vaccine
    - 9vHPV vaccine is indicated in girls/women 9-45 years of age (Canada, Australia), and individuals from the age of 9 years (European Union)
  - The European Medicines Agency requested a clinical study to compare 9vHPV vaccine safety and immunogenicity in women 27-45 y/o versus women 16-26 y/o as a post-licensure commitment

High Efficacy of qHPV vaccine Across the Entire 24-45 Year Age Range in the FUTURE III Study

Per-protocol Efficacy Population

- *In the FUTURE III study, efficacy of qHPV vaccine was high in both the 24- to 34-year and the 35-to 45-years age strata (ref.: Castellsague et al. Br J Cancer 2011; 105:28-37)*

Endpoint	qHPV Vaccine Cases	Placebo Cases	Efficacy (95% CI)
HPV6/11/16/18-related 6-month persistent infection, CIN, and condyloma			
• Overall	10	86	88.7% (78.1, 94.8)
• 24- to 34-year-olds	5	56	91.3% (78.4, 97.3)
• 35- to 45-year-olds	5	30	83.8% (57.9, 95.1)
HPV6/11/16/18-related Pap test abnormalities*			
• Overall	1	38	97.4% (84.5, 99.9)
• 24- to 34-year-olds	1	25	95.9% (75.1, 99.9)
• 35- to 45-year-olds	0	13	100% (68.0, 100)

*ASC-US HR-HPV positive or worse

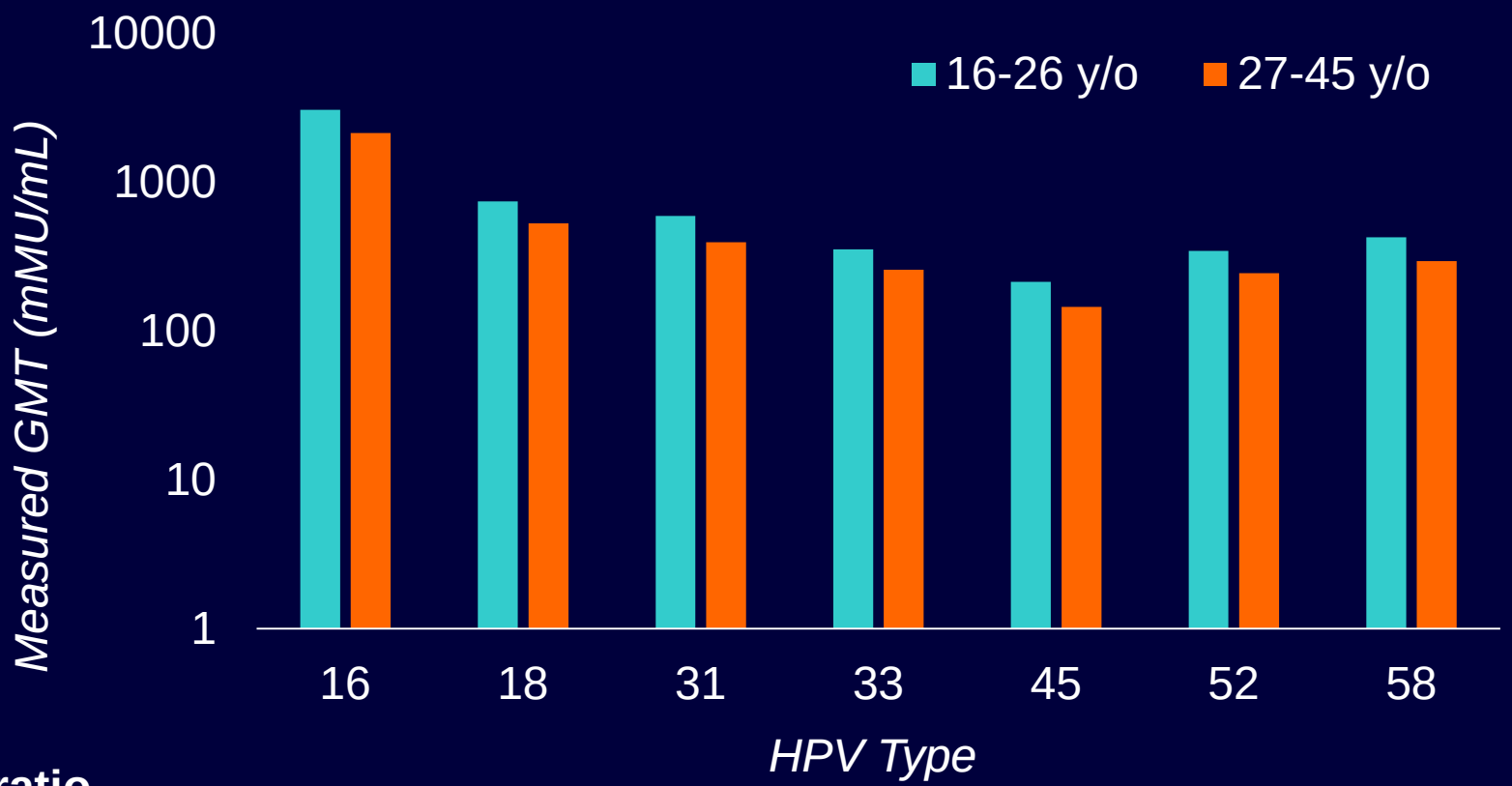
9vHPV Vaccine Immunogenicity Study in Women 27-45 Years of Age (Protocol 004)

Enrollment	• 642 women, 27- to 45-year-old • 570 women, 16- to 26-year-old (control group)
Vaccine administration	Open-label, 7-month study All participants receive 9vHPV vaccine at Day 1, and Months 2 and 6
Follow-up	<u>Immunogenicity</u> • Serum samples for anti-HPV titers (Day 1 and Month 7) <u>Safety</u> • Injection-site and systemic AEs (days 1 to 15 post-vaccination) • SAEs: entire study duration (7 months)
Study objectives	• Non-inferior* Month 7 GMTs for the 7 high-risk types** in 27- to 45-year-olds versus 16- to 26-year-olds • Summarize GMTs and seroconversion rates for all 9 HPV types • Acceptable safety profile

*The non inferiority criterion requires a <2-fold decrease in immunogenicity in older vs. younger women
**The 7 high-risk types in the 9vHPV vaccine are HPV16, 18, 31, 33, 45, 52, and 58.

Protocol 004: Non-inferior GMT at Month 7: Women 27-45 Years of Age vs. Women 16-26 Years of Age

The non-inferiority criterion was met for all 7 high-risk HPV types (all p<0.001)*



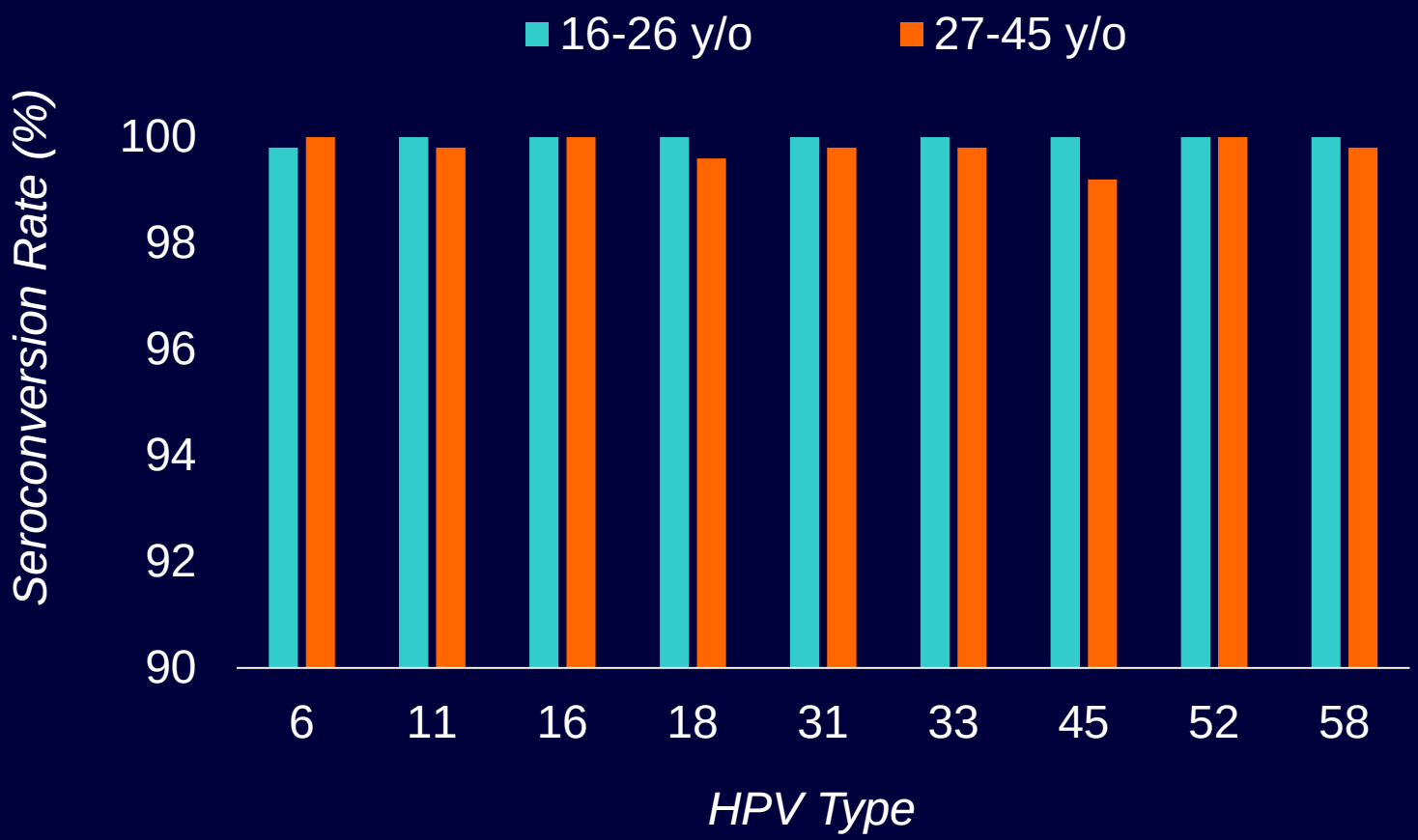
	16	18	31	33	45	52	58
GMT ratio 27-45 y/o / 16-26 y/o	**0.70**	**0.71**	**0.66**	**0.73**	**0.68**	**0.71**	**0.69**
(95% CI)	(0.63, 0.77)	(0.64, 0.80)	(0.60, 0.74)	(0.67, 0.80)	(0.60, 0.76)	(0.64, 078)	(0.63, 076)

Merck unpublished data

* The non inferiority criterion requires that the lower bound of the 95% CI of GMT ratio 27-45 y/o / 16-26 y/o be >0.5.

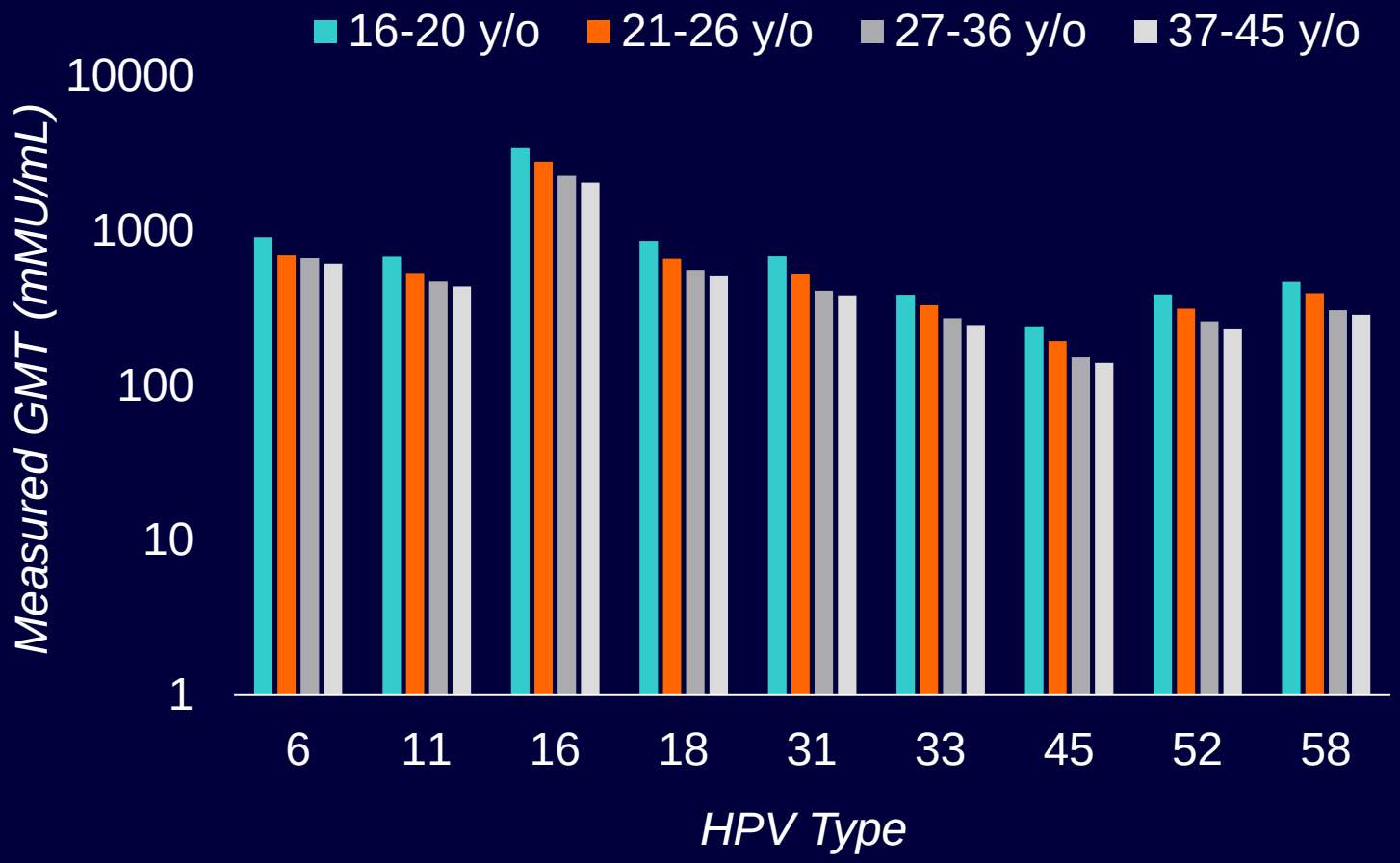
Protocol 004: High Seroconversion Rates at 1 Month Post-Last Dose in 27-45 y/o Women vs. 16-26 y/o Women Vaccinated with 9vHPV Vaccine

Seropositivity rates at Month 7 were >99% for the 9 HPV types



Protocol 004: GMT at 1 Month Post-Last Dose in 16-45 y/o Women Vaccinated with 9vHPV Vaccine: Analysis by Age Strata

GMTs tend to decrease with age at vaccination
(consistent with previous observations with qHPV vaccine)



Protocol 004: AE Summary
(Day 1 to Month 7)

AE	27-45 y/o (N=640)	16-26 y/o (N=570)
Subjects with AEs	n (%)	n (%)
Injection-site	547 (85.5)	501 (87.9)
Systemic Vaccine-related*	414 (64.7) 154 (24.1)	380 (66.7) 143 (25.1)
Serious AEs Vaccine-related* Deaths	8 (1.3) 0 (0.0) 0 (0.0)	6 (1.1) 0 (0.0) 0 (0.0)
Discontinuation due to an AE Due to a vaccine-related* AE Due to a serious AE	1 (0.2) 0 (0.0) 0 (0.0)	0 (0.0) 0 (0.0) 0 (0.0)

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

Protocol 004: Injection-site AEs (Incidence ≥1%)
(Days 1 to 5 Following Any Vaccination)

Injection-site AE	27-45 y/o (N=640)	16-26 y/o (N=570)	Difference in % vs. 16-26 y/o
	n (%)	n (%)	Estimate (95% CI)
Pain	530 (82.8)	491 (86.1)	-3.3 (-7.4, 0.8)
Swelling	149 (23.3)	133 (23.3)	-0.1 (-4.9, 4.7)
Erythema	108 (16.9)	111 (19.5)	-2.6 (-7.0, 1.7)
Pruritus	10 (1.6)	10 (1.8)	-0.2 (-1.8, 1.3)
Hematoma	8 (1.3)	6 (1.1)	0.2 (-1.2, 1.5)
Discomfort	5 (0.8)	7 (1.2)	-0.4 (-1.8, 0.8)
Bruising	5 (0.8)	6 (1.1)	-0.3 (-1.6, 0.9)

Conclusions

- Most women 27-45 years of age are susceptible to infection by HPV types covered by the 9vHPV vaccine
- The qHPV vaccine
  - Is highly efficacious in women 16-45 years of age, regardless of age
  - Provides durable protection (up to at least 10 years)
- The 9vHPV vaccine
  - Is highly immunogenic in women 27-45 years of age
    - Seroconversion rates >99% for the 9 HPV types
  - Induces HPV antibody responses in women 27-45 years of age that are non-inferior to responses in women 16-26 years of age
    - Efficacy in women 27-45 years of age was previously inferred based on the overall qHPV and 9vHPV vaccine clinical data
    - This result further supports the efficacy of the 9vHPV vaccine in women 27-45 years of age
  - Is generally well tolerated in women 27-45 years of age
- This supports the clinical benefit of the 9vHPV vaccine in 27- 45-year-olds