9vHPV Vaccine for Mid-Adult Persons (27-45 yo) Results from Clinical Studies

Advisory Committee on Immunization Practices

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Introduction – 9-valent HPV (9vHPV) Vaccine

- 9vHPV vaccine was licensed for use in 9-26 year olds of both genders
- In 2015, ACIP:
  - Included 9vHPV vaccine in its recommendations for routine HPV vaccination of girls and boys 11-12 years
  - Recommended catch-up vaccination for males up to age 21 years, and for females, MSM and immunocompromised persons (including those with HIV infection) up to age 26 years

- A supplementary application to expand the age indication for 9vHPV vaccine was filed with the FDA in April 2018
  - Current age indication: 9-26 years (males and females)
  - Proposed new age indication: 9-45 years (males and females)*
  - Expected review time up to 6 months

**The 9vHPV vaccine is indicated in girls and women 9-45 years of age in Canada and Australia, and individuals from the age of 9 years in the European Union*

Clinical Studies Supporting HPV Vaccination of Adults 27-45 Years of Age

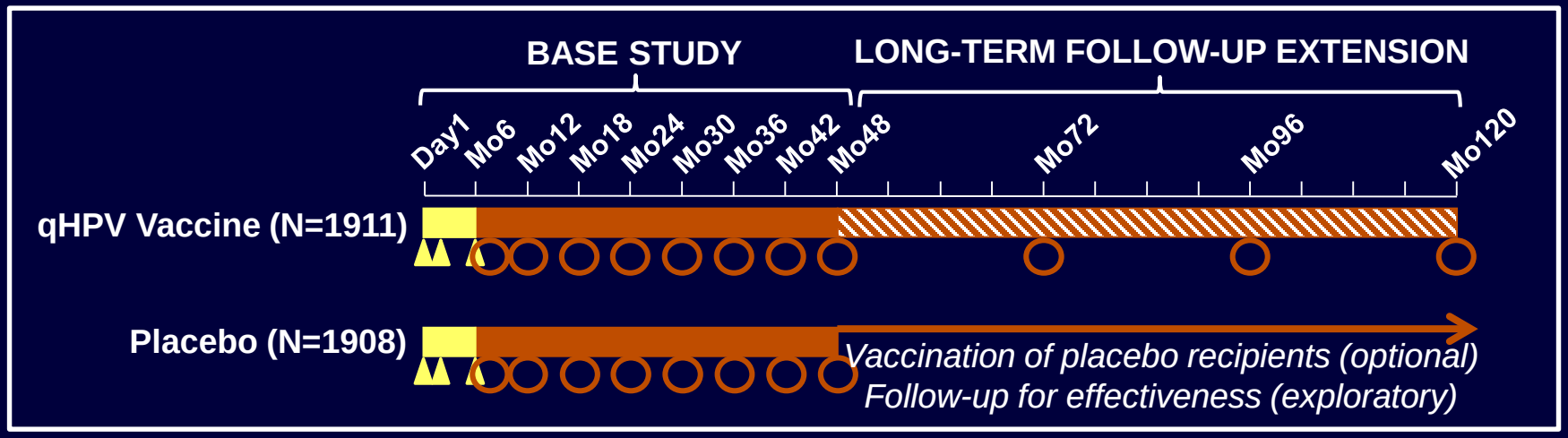
- The proposed licensure for use of 9vHPV vaccine among 27- 45-year-olds is based on a Phase 3 study of qHPV vaccine
  - High prophylactic efficacy among 27- to 45-year-old women
  - Durable effectiveness through 10 years of follow-up

- Regulatory agencies have concluded that qHPV vaccine efficacy/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

QHPV VACCINE MID-ADULT STUDIES

qHPV Vaccine 10-year Study in 24-45 Year-Old Women

(Protocol V501-019 – NCT00090220)



STUDY STAGE

- **Vaccination period**
- **Efficacy follow-up period (base study)**
- **Effectiveness follow-up period (extension)**
  - *Subset of subjects from Colombia (N=685)*

KEY ACTIVITIES

- **Vaccine/placebo administration**
- **Follow-up visits**
  - *Serum collection (immunogenicity)*
  - *Cervical cytology (Pap test)*
  - *Genital swab (HPV DNA; base study only)*

Reference: Luna et al. PLoS One 2013; 8:e83431

Base Study: Baseline Characteristics of Randomized Subjects

	qHPV Vaccine (N=1911)	Placebo (N=1908)
	n (%)	n (%)
Mean Age (years ± sd)	34.3 ± 6.3	34.3 ± 6.3
Lifetime no. of sexual partners		
1	713 (37.6)	751 (39.4)
2	385 (20.2)	362 (19.0)
3	229 (12.0)	223 (11.7)
4	142 (7.4)	130 (6.8)
>4	433 (22.7)	437 (22.9)
Median	2	2
Baseline HPV DNA prevalence		
All vaccine types	159 (8.4)	139 (7.4)
HPV 6	34 (1.8)	37 (1.9)
HPV 11	4 (0.2)	5 (0.3)
HPV 16	93 (4.9)	77 (4.0)
HPV 18	39 (2.0)	40 (2.1)

N=number of subjects randomized

Reference: Castellsague et al. Br J Cancer. 2011;105:28-37

Base Study: HPV6/11/16/18-related Persistent Infection (PI), Cervical Disease (CIN), and Condyloma

(*24-45 yo women*; *Per Protocol Efficacy Population)*

Endpoint	qHPV Vaccine (N=1910)	Placebo (N=1907)	Efficacy (95% CI)
	Cases/ n	Cases/ n	
6-month PI	**9** / 1581	**85** / 1586	**89.6%** (79.3, 95.4)
CIN (any grade)	**1** / 1581	**17** / 1584	**94.1%** (62.5, 99.9)
≥ CIN 2	**1** / 1581	**6** / 1584	**83.3%** (-37.6, 99.6)
Condyloma	**0** / 1600	**7** / 1599	**100%** (30.8, 100)

End-of-base study analyses (mean follow-up: 3.8 years)

N=number of subjects randomized who received ≥1 injection
n=number of subjects who had ≥1 follow-up visit after Month 7

Reference: Castellsague et al. Br J Cancer. 2011;105:28-37

Base Study: Vaccine-related AEs (24-45 yo Women)

Type of AE	qHPV Vaccine (N=1889)	Placebo (N=1886)
	n (%)	n (%)
Number (%) of subjects		
With injection-site AE*	1443 (76.4)	1210 (64.2)
Injection-site pain	1423 (75.3)	1170 (62.0)
Severe	60 (3.2)	33 (1.7)
Injection-site swelling	353 (18.7)	214 (11.3)
Severe (>2 inches)	28 (1.5)	14 (0.7)
Injection-site erythema	273 (14.5)	200 (10.6)
Severe (>2 inches)	11 (0.6)	6 (0.3)
With vaccine-related systemic AE**	745 (39.4)	695 (36.9)
Headache	401 (21.2)	375 (19.9)
Pyrexia	178 (9.4)	170 (9.0)
With serious AE***	0 (0.0)	0 (0.0)
Who discontinued due to an AE**	5 (0.3)	1 (0.1)

Based on a visit cut-off date of 13-Jul-2007
N=number of subjects who received ≥1 injection and had safety follow-up
*Days 1-5 after any vaccination; **Days1-15 after any vaccination; ***Entire study duration

Long Term Follow-up Extension: Data Analysis [1 of 2]

- When the base study was finished, placebo-recipients were offered vaccine
- A cohort of 685 Colombian subjects who received qHPV vaccine in the base study consented to participate in a long-term extension for a total of 10 years of follow-up
  - 651 Colombian subjects who received placebo in the base study and qHPV vaccine after the base study were also followed in the extension for exploratory analyses
- Vaccine effectiveness was evaluated in these subjects
  - Primary effectiveness endpoint: HPV6/11/16/18-related CIN or condyloma
  - Primary analysis population: per-protocol effectiveness population
    - Received 3 doses of qHPV vaccine within 1 year in the base study
    - Seronegative at Day 1 and PCR negative Day 1 through Month 7 for the HPV type being analyzed
  - The cumulative probabilities of acquiring the primary endpoint in the primary analysis population during the relevant study periods were calculated

Long Term Follow-up Extension: Data Analysis [2 of 2]

- The overall study was conducted in women 24-45 years at enrollment
- 9vHPV vaccine is recommended in girls/women 9-26 years; therefore, the analyses are presented only in women 27-45 years at enrollment
  - 600 subjects 27-45 year old at enrollment who received qHPV vaccine in the base study and continued in the LTFU study
  - Follow-up for effectiveness of these subjects (in the base study and LTFU study combined) up to 10.1 (median: 8.9) years post-dose 3

Efficacy of qHPV Vaccine in Women 27-45 Years at Enrollment in the Base Study

Per-protocol Efficacy Population

Endpoint	qHPV Vaccine (N=1624)	Placebo (N=1629)	Efficacy (95% CI)
	Cases/ n	Cases/ n	
HPV6/11/16/18-related CIN, and condyloma	**1** / 1376	**20** / 1384	**95.0%** (68.7, 99.9)

End-of-base study analyses (median follow-up: 3.9 years)
N=number of subjects randomized who received ≥1 injection
n=number of subjects who had ≥1 follow-up visit after Month 7

Cumulative Incidence of HPV6/11/16/18-related CIN or Condyloma in 4-Year Intervals of LTFU Study vs Base Study

(27-45 yo at Day 1; Per Protocol Efficacy Population)

Time from Dose 1	qHPV Vaccine in base study (N=1624)		Placebo in base study (N=1629)	
	Cases/ n	Cumulative Incidence Probability Estimate*† (95% CI)	Cases/ n	Cumulative Incidence Probability Estimate*† (95% CI)
Day 1 to Year 4				
All subjects	**1** / 1377	**0.7 (0.1, 5.2)**	**16** / 1384	**12.1 (7.4, 19.7)**
Non-Colombia	**1** / 778	**1.3 (0.2, 9.2)**	**5** / 759	**6.8 (2.8, 16.2)**
Colombia	**0** / 599	**0.0**	**11** / 625	**17.9 (10.0, 32.2)**
Year 4 to Year 8	**0** / 804	**0.0**	–	–
Year 6 to Year 10	**0** / 527	**0.0**	–	–

**Cumulative incidence probability expresses the probability (in the population) of acquiring the disease endpoint during the time interval indicated in the corresponding row.*

† In 10^{-3} units (e.g., 0.7 in 10^{-3} units= 0.0007)

Cumulative Incidence of HPV31/33/35/39/45/51/52/56/58/59-related CIN or Condyloma in 4-Year Intervals of LTFU Study vs Base Study

(27-45 yo at Day 1; Naïve to the Relevant HPV Type Population)

Time from Dose 1	qHPV Vaccine in base study (N=1624)		Placebo in base study (N=1629)	
	Cases/ n	Cumulative Incidence Probability Estimate*† (95% CI)	Cases/ n	Cumulative Incidence Probability Estimate*† (95% CI)
Day 1 to Year 4				
All subjects	**26** / 1586	**17.8 (12.1, 26.0)**	**27** / 1578	**18.5 (12.7, 26.9)**
Non-Colombia	**11** / 907	**14.2 (7.8, 25.7)**	**10** / 887	**12.1 (6.5, 22.4)**
Colombia	**15** / 679	**22.8 (13.8, 37.6)**	**17** / 691	**25.4 (15.8, 40.5)**
Year 4 to Year 8	**3** / 888	**4.8 (1.3, 13.3)**	**–**	**–**
Year 6 to Year 10	**4** / 576	**10.8 (3.4, 27.3)**	**–**	**–**

**Cumulative incidence probability expresses the probability (in the population) of acquiring the disease endpoint during the time interval indicated in the corresponding row.*

† In 10^{-3} units (e.g., 17.8 in 10^{-3} units= 0.0178)

Summary of 10-year Study of qHPV Vaccine in Women 27-45 Years

- Durable effectiveness through 10 years
  - No cases of HPV6/11/16/18-related cervical disease and condyloma during the study extension
  - Continued exposure to non-vaccine HPV types (absence of HPV disease is not due to lack of HPV exposure)
  - Follow-up through 10.1 years (median 8.9 years)
- Sustained immunogenicity through 10 years post vaccination onset
- qHPV vaccine generally well-tolerated
  - No vaccine-related serious AE during the entire study

Post-hoc Immunogenicity Bridging Analyses Cross-study Comparison of qHPV Vaccine Trials

STUDIES INCLUDED IN THE ANALYSES

Study	Population
Protocol V501-013 (aka FUTURE I)	16-26 yo women
Protocol V501-015 (aka FUTURE II)	16-26 yo women
Protocol V501-019 (aka FUTURE III)	24-45 yo women
Protocol V501-020	16-26 yo men
Protocol V501-108 (aka the MAM study)	27-45 yo men

References:

- V501-013 (NCT00092521): Garland et al. N Engl J Med. 2007;356:1928–1943
- V501-015 (NCT00092534): FUTURE II Study Group. N Engl J Med. 2007;356:1915–1927
- V501-019 (NCT00090220): Muñoz et al. Lancet. 2009;373:1949–1957
- V501-020 (NCT00090285): Giuliano et al. N Engl J Med. 2011;364:401–411
  Palefsky et al. N Engl J Med. 2011;365:1576–1585
- V501-108 (NCT01432574): Giuliano et al. (2015) Vaccine 33:5640-5646.

Post-hoc Immunogenicity Bridging Analyses Cross-study Comparison of qHPV Vaccine Trials

- **Objective**
  - Comparison of HPV6, 11, 16, and 18 GMTs at 1 month post-dose 3 between 27-45 year-olds and 16-26 year-olds
  - Non-inferiority criterion: lower bound of the 95% CI of the GMT ratio (27-45 yo / 16-26 yo) >0.67

- **Populations analyzed**
  - Women
    - ✓ 27-45 yo women from FUTURE III
    - ✓ 16-26 yo women pooled from FUTURE I, FUTURE II, and FUTURE III
  - Men
    - ✓ 27-45 yo men from Protocol V501-108 (aka the MAM Study)
    - ✓ 16-26 yo men from Protocol V501-020

Non-inferior GMTs at Month 7 in 27-45 yo Women vs. 16-26 yo Women who Received qHPV Vaccine

Assay (cLIA)	27-45 yo women (Group A)		16-26 yo women (Group B)		Group A / Group B
	n	GMT	n	GMT	GMT ratio (95% CI)
Anti-HPV 6	1083	412.4	2800	536.2	0.77 (0.72, 0.82)
Anti-HPV 11	1083	538.2	2824	754.3	0.71 (0.67, 0.76)
Anti-HPV 16	1092	2212.0	2749	2297.6	0.96 (0.89, 1.05)
Anti-HPV 18	1223	348.4	3006	458.1	0.76 (0.71, 0.82)

Conclusions: non-inferiority was demonstrated for the 4 HPV types; based on these results, efficacy results previously established in 16-26 yo women are extended to 27-45 yo women

Non-inferior GMTs at Month 7 in 27-45 yo Men vs. 16-26 yo Men who Received qHPV Vaccine

Assay (cLIA)	27-45 yo men (Group A)		16-26 yo men (Group B)		Group A / Group B
	n	GMT	n	GMT	GMT ratio (95% CI)
Anti-HPV 6	147	420.0	1092	447.6	0.94 (0.76, 1.15)
Anti-HPV 11	147	514.5	1092	624.0	0.82 (0.70, 0.98)
Anti-HPV 16	147	2481.3	1135	2404.3	1.03 (0.85, 1.26)
Anti-HPV 18	147	302.6	1174	402.3	0.75 (0.61, 0.93)

Conclusions: non-inferiority was demonstrated for HPV types 6, 11, and 16; based on these results, efficacy results previously established in 16-26 yo men are extended to 27-45 yo men

SIMILAR EFFICACY, IMMUNOGENICITY, AND SAFETY OF 9vHPV AND qHPV VACCINES IN 9 TO 26 YEAR OLDS

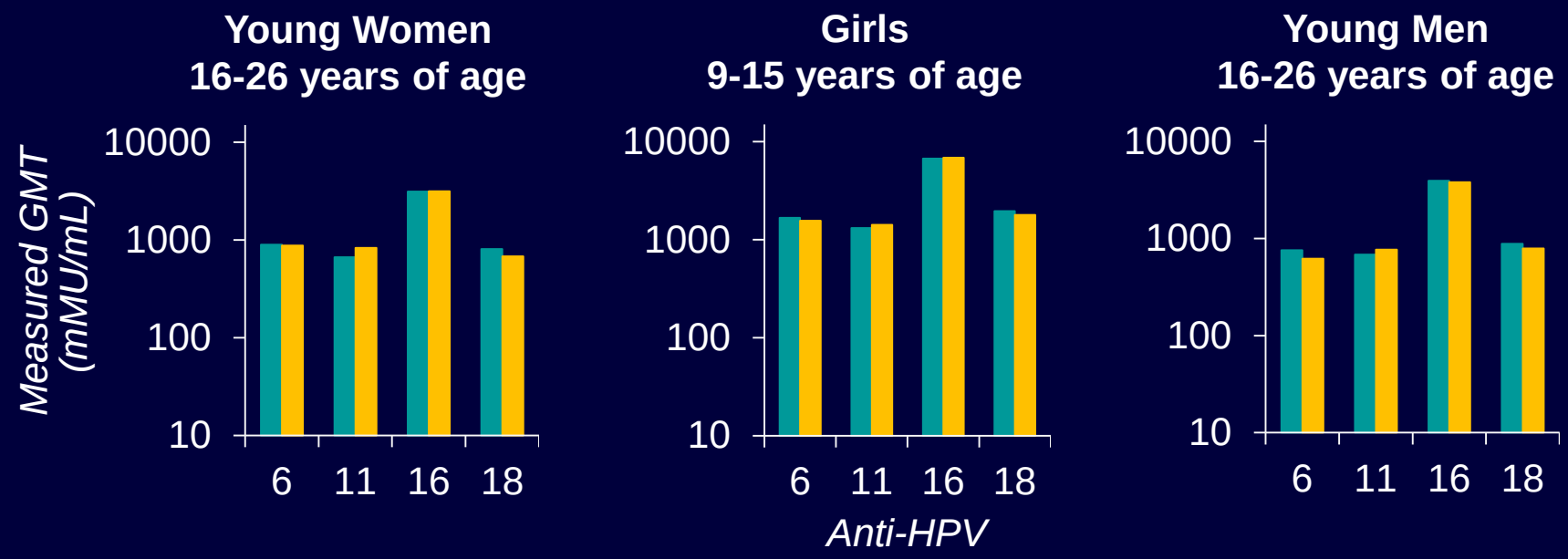
Bridging Efficacy, Immunogenicity and Safety Across Vaccines and Across Genders

- Efficacy of qHPV vaccine against HPV6/11/16/18-related disease
  - ✓ Demonstrated in clinical studies in women16-26 years, women 27-45 years and men 16-26 years
- Efficacy of 9vHPV vaccine against HPV6/11/16/18-related disease
  - ✓ Inferred based on non-inferior HPV6/11/16/18 antibody response in 9vHPV vaccine group vs. qHPV vaccine group (regardless of age and gender)
  - ✓ Further supported by observation of similar, low incidence of HPV6/11/16/18-related disease in a clinical study in 16-26 yo women
- Generally comparable adverse event profile with 9vHPV and qHPV vaccine
  - ✓ More injection-site AEs, mostly mild or moderate in intensity
  - ✓ Adverse events less frequent in men than in women

Ref: Luxembourg A, Moeller E. Expert Rev Vaccines 2017; ***16****: 1119–39.*

Non-inferiority of Month 7 cLIA GMT in 9vHPV Vaccine Group vs. qHPV Vaccine Group

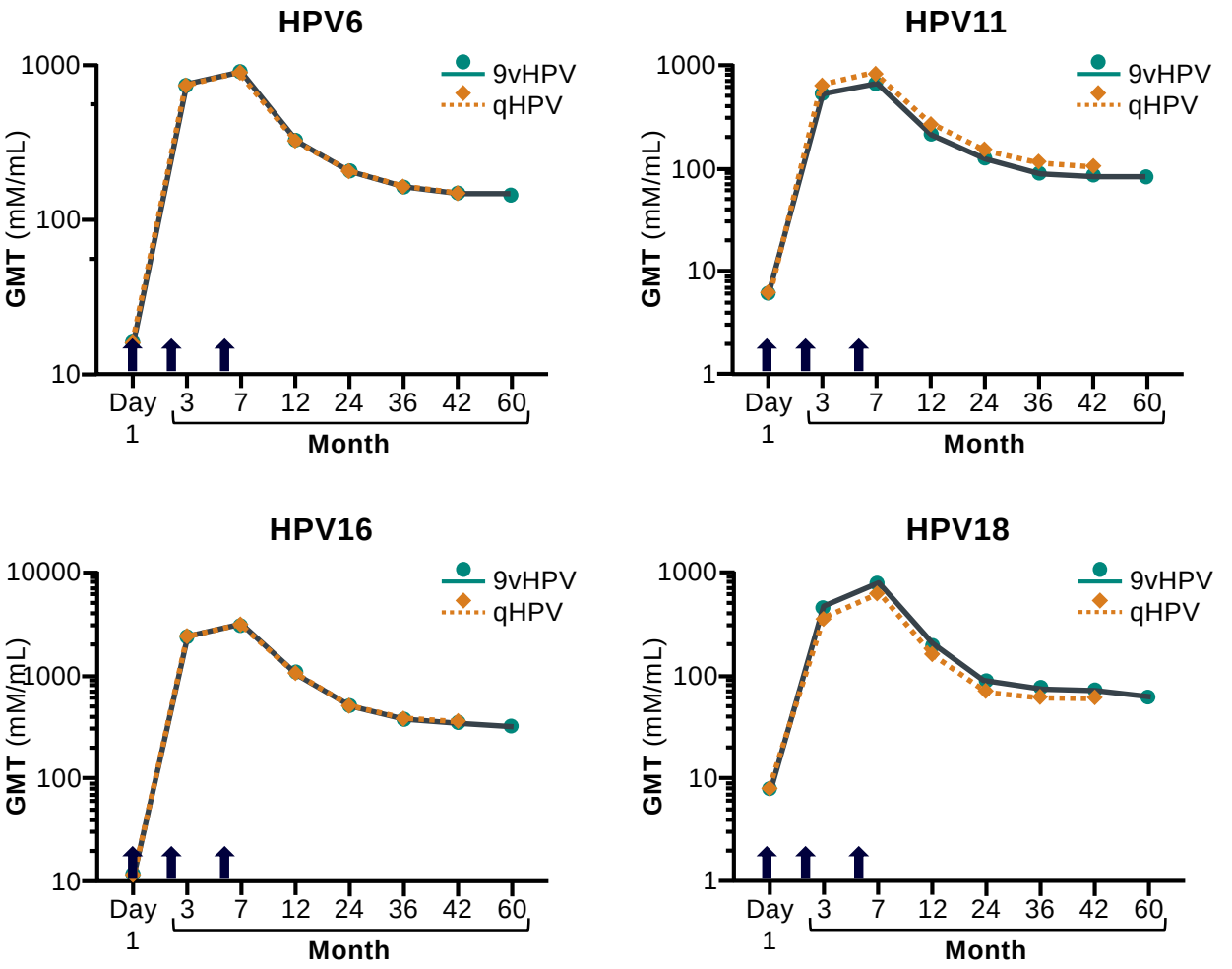
- Three clinical studies in 3 demographic groups showed non-inferior immunogenicity of 9vHPV vaccine versus qHPV vaccine
  - *Comparison at month 7 (1 month post-dose 3) for all 3 studies (see below)*
  - *Assessment over time in young women 16-26 years of age (next slide)*



Joura et al. N Engl J Med. 2015;372:711–723
Vesikari et al. Pediatr Infect Dis J. 2015;34:992–998
Van Damme et al. Vaccine. 2016;34:4205–4212.

Similar HPV6/11/16/18 Antibody Response Profiles for 9vHPV Vaccine and qHPV Vaccine Over Time

(Women 16-26 years of age)



⬆: Vaccination visits at Day 1, Month 2, and Month 6.

Reference:
Huh et al. Lancet 2017; 390:2143-2159

Similar Protection Against HPV6/11/16/18 Disease Endpoints with 9vHPV Vaccine and qHPV Vaccine

16-26 yo women – Per-Protocol Efficacy Population

Endpoint	9vHPV vaccine clinical program*		qHPV vaccine clinical program**	
	9vHPV	qHPV	qHPV	Placebo
	Cases/total	Cases/total	Cases/total	Cases/total
Low-grade cervical disease	**0** / 5824	**2** / 5832	**7** / 7629	**168** / 7632
High-grade cervical disease	**1** / 5824	**1** / 5832	**2** / 7864	**110** / 7865
High-grade vulvar disease	**0** / 5876	**0** / 5893	**0** / 7900	**13** / 7902
High-grade vaginal disease	**0** / 5876	**2** / 5893	**0** / 7900	**10** / 7902
Genital warts	**5** / 5876	**2** / 5893	**2** / 7665	**190** / 7669

**Based on up to 67 months of follow-up post-dose 3 (median 43 months)*

***Based on average of 42 months of follow-up post-dose 3*

References: FUTURE I/II Study Group BMC 2010; 341:c3493; Kjaer et al. Cancer Prev Res (Phila); 2009;2:868–878; Huh et al. Lancet 2017; 390:2143-2159.

CONCLUSIONS

Conclusions

- Efficacy/effectiveness
  - qHPV vaccine prevents HPV6/11/16/18-related CIN and condyloma through at least 10 years post vaccination in women 27-45 years of age
- Immunogenicity
  - qHPV vaccine elicits HPV6/11/16/18 antibody responses in women and men 27-45 years of age that are non-inferior to antibody responses in women and men 16-26 years of age
    - These results support efficacy in women and men 27-45 years of age
- Safety
  - qHPV vaccine is generally well tolerated in women/men 27-45 years of age
- Relevance to 9vHPV vaccine
  - Clinical experience with qHPV vaccine is relevant to 9vHPV vaccine
    - Consistent immunogenicity, efficacy, and safety profile of the 2 vaccines
    - Both vaccines contain VLPs for HPV6/11/16/18 and are manufactured using similar processes
  - Therefore, these results are deemed applicable to 9vHPV vaccine

Ongoing 9vHPV Vaccine Study

- Protocol V503-004 (CT.gov identifier: NCT03158220)
  - Post-marketing study requested by the EMA
- Study population
  - 27-45 yo women (N=600)
  - 16-26 yo women (N=600) (control group)
- Vaccine administration
  - 9vHPV vaccine; standard 3-dose regimen (day 1, months 2 and 6)
- Primary objective
  - Demonstrate non-inferior GMT at Month 7 in 27-45 yo women versus 16-26 yo women for the 7 high-risk types in the vaccine
- Timeline
  - Analyses expected in 2Q2019