Immunogenicity and tolerability of HPV vaccine in women aged 15-55: Study findings and way forward

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Conflict of interest 2019

- Honoraria for lecturing from Pfizer, GSK, MSD, Roche, Biogen
- Honoraria as member of advisory boards from Pfizer and GSK
- Honoraria for clinical trials from GSK and Pfizer
Methods

• Study design: long-term (10-year) follow-up study (HPV-014 EXT; NCT00947115) of a phase III, multi-centre, open-label study (HPV-014; NCT00196937)

• Participants: women aged 15–55 years at the time of vaccination who received 3 doses of AS04-HPV-16/18 Vaccine (at months 0, 1, 6) in HPV-014; study sites in Germany and Poland

• Measurements:
  – Serum and cervico-vaginal secretions (CVS) anti-HPV-16/18 antibody responses were assessed by enzyme-linked immunosorbent assay (ELISA)
  – Samples were collected at years 5, 6, 7, 8, 9, 10
  – Safety was assessed throughout the study

• Analyses: participants were stratified by age at vaccination: 15–25, 26–45, 46–55 years

PERSISTENCE OF IMMUNE RESPONSE 10 YEARS AFTER ADMINISTRATION OF THE HUMAN PAPILLOMAVIRUS (HPV)-16/18 AS04-ADJUVANTED VACCINE TO WOMEN AGED 15–55 YEARS EUROGIN 2016;
Seropositivity rates in serum at Year 10

In initially seronegative women (Year 10 ATP cohort for immunogenicity)

<table>
<thead>
<tr>
<th>Age group</th>
<th>≥cut-off* for anti-HPV 16 VLP IgG, n/N (% [95% CI])</th>
<th>≥cut-off† for anti-HPV 18 VLP IgG, n/N (% [95% CI])</th>
</tr>
</thead>
<tbody>
<tr>
<td>15–25 years</td>
<td>123/123 (100 [97.0–100])</td>
<td>126/127 (99.2 [95.7–100])</td>
</tr>
<tr>
<td>26–45 years</td>
<td>120/121 (99.2 [95.5–100])</td>
<td>133/142 (93.7 [88.3–97.1])</td>
</tr>
<tr>
<td>46–55 years</td>
<td>103/107 (96.3 [90.7–99.0])</td>
<td>109/130 (83.8 [76.4–89.7])</td>
</tr>
</tbody>
</table>

*Assay cut-off 19 EU/mL
†Assay cut-off 18 EU/mL
ATP, according to protocol; CI, confidence interval; VLP, virus-like particle

Antibody Levels in 15-55 Year Olds Comparable to those Observed in Efficacy Study HPV-001/007

ATP analysis
Seronegative prior to vaccination


Assay cut-off: 8 EU/ml
Antibody Levels in 15-55 Year Olds Comparable to those Observed in Efficacy Study HPV-001/007

At least 8-fold higher than natural infection

15–25 years Efficacy study
15–25 years
26–35 years
36–45 years
46–55 years

Natural Infection

Assay cut-off: 7 EU/ml

ATP analysis
Seronegative prior to vaccination

**Anti-HPV-16 VLP IgG GMTs in serum**

In initially seronegative women (Year 10 ATP cohort for immunogenicity)

### Years after vaccination
- **15-25 years**
- **26-45 years**
- **46-55 years**

#### Year 10
- 965 (95% CI 802–1162)
- 334 (95% CI 271–414)
- 157 (95% CI 128–193)

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PERSISTENCE OF IMMUNE RESPONSE 10 YEARS AFTER ADMINISTRATION OF THE HUMAN PAPILLOMAVIRUS (HPV)-16/18 AS04-ADJUVANTED VACCINE TO WOMEN AGED 15–55 YEARS EUROGIN 2016;
Anti-HPV-18 VLP IgG GMTs in serum

In initially seronegative women (Year 10 ATP cohort for immunogenicity)

Years after vaccination

Year 10
321 (95% CI 265–389)
115 (95% CI 94–142)
70 (95% CI 56–87)

Plateau level
Natural infection level

HPV-18 GMT (EL.U/mL) (95% CI)

15-25 years
26-45 years
46-55 years


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Correlations between serum and CVS anti-HPV-16/18 antibodies*

**Standardised for total IgG (Year 10 TVC)**

*No statistical testing was performed

PERSISTENCE OF IMMUNE RESPONSE 10 YEARS AFTER ADMINISTRATION OF THE HUMAN PAPILLOMAVIRUS (HPV)-16/18 AS04-ADJUVANTED VACCINE TO WOMEN AGED 15–55 YEARS EUROGIN 2016
Prediction of antibody responses

Piecewise model

Modified power-law

Serum neutralising antibodies (PBNA) at Month 60 (M60 ATP cohort*)

**HPV-16**

<table>
<thead>
<tr>
<th>Age groups (years)</th>
<th>GMT (ED(_{50})) [95% CI]</th>
<th>Natural infection</th>
<th>HPV-16/18 vaccine</th>
<th>HPV-6/11/16/18 vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>18–26</td>
<td>100% 100% 100% (100% 97.5% 100%)</td>
<td>100% 97.5% 100% (100% 97.5% 100%)</td>
<td>100% 97.5% 100% (100% 97.5% 100%)</td>
<td>100% 97.5% 100% (100% 97.5% 100%)</td>
</tr>
<tr>
<td>27–35</td>
<td>100% 100% 100% (100% 96.6% 100%)</td>
<td>100% 96.6% 100% (100% 96.6% 100%)</td>
<td>100% 96.6% 100% (100% 96.6% 100%)</td>
<td>100% 95.7% 100% (100% 95.7% 100%)</td>
</tr>
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</tr>
</tbody>
</table>

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Serum neutralising antibodies (PBNA) at Month 60 (M60 ATP cohort*)

**HPV-18**

<table>
<thead>
<tr>
<th>Age groups (years)</th>
<th>GMR (95% CI)</th>
<th>GMR (95% CI)</th>
<th>GMR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18–26</td>
<td>12.07 (6.60, 22.08)</td>
<td>13.00 (7.59, 22.25)</td>
<td>7.76 (4.53, 13.29)</td>
</tr>
</tbody>
</table>

**Einstein MH et al. Hum Vaccin Immunother. 2014;10(12):3435-45.**
Serum neutralising antibodies (PBNA): kinetic cohorts* (all age groups)

*Kinetic cohort = sub-cohort of the M60 according-to-protocol cohort for immunogenicity that includes seronegative and DNA-negative subjects at baseline with available and valid results for the HPV type analysed at each time point. ED50 = serum dilution giving a 50% reduction of the signal compared with a control. PBNA, pseudovirion-based neutralisation assay. Natural infection = 180.1 ED50 and 137.3 ED50 for HPV-16 and -18 neutralising antibodies, respectively (Einstein et al., Hum Vacc 2009; 7:1343-1358).

Safety during the entire 10-year study period

Year 10 TVC

• Fatal adverse events
  – 1 chronic lymphocytic leukaemia (considered not vaccine related)
  – 1 malignant lung neoplasm (considered not vaccine related)

• Serious adverse events considered related to vaccine
  – 1 cervical dysplasia at Year 8 (subject was HPV-16 seropositive and unknown DNA status before vaccination). The subject recovered

TVC, total vaccinated cohort

PERSISTENCE OF IMMUNE RESPONSE 10 YEARS AFTER ADMINISTRATION OF THE HUMAN PAPILLOMAVIRUS (HPV)-16/18 AS04-ADJUVANTED VACCINE TO WOMEN AGED 15–55 YEARS EUROGIN 2016
Conclusions

Immunogenicity up to 10 years after first vaccination with HPV-16/18 vaccine was sustained in women aged 15–55 years at vaccination\textsuperscript{1,2}

- $\geq 96.3\%$ seropositivity for anti-HPV-16 antibodies
- $\geq 83.8\%$ seropositivity for anti-HPV-18 antibodies

Antibody GMTs at year 10 were\textsuperscript{1,2}

- $\geq 70$ EL.U/mL, with an age at vaccination-dependant decrease in serum antibody levels

Among those aged 15–25 years, similar to or above the plateau level observed in studies where vaccine efficacy was demonstrated in those aged 15–25 years

Among the older age groups, similar to or below this plateau level above natural infection levels (as determined in unvaccinated women who had cleared an infection)

Good correlation between antibodies (IgG) in the serum and in the CVS indicates likely transudation to the cervical epithelium\textsuperscript{1,2}

The 10-year safety profile of HPV-16/18 vaccine was acceptable\textsuperscript{1,2}

The difference in serum neutralising antibody response to HPV-16 and -18 observed at Month 7 between the two prophylactic HPV vaccines was sustained up to Month 60\textsuperscript{3}