Development of the HPV 16 / 18 Cervical Cancer Vaccine

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Director – Medical Affairs – N.A.
Cervical Cancer Vaccines
August 3, 2006
Overview

- GSK Biologicals
- Search for a cervical cancer vaccine
- GSK HPV 16/18 candidate vaccine
  - Novel adjuvant system resulting in strong and sustained immune responses
  - Focus on cervical cancer prevention
- Clinical trial data
  - Efficacy data
  - Immunogenicity data
  - Broad oncogenic protection
- Current status of the GSK HPV 16/18 candidate vaccine
GlaxoSmithKline Biologicals: One of the World’s Leaders in Vaccines

Total market*: $8 billion

- AP/AP-MSD: 26%
- GSK: 23%
- Merck: 19%
- Wyeth-Ayerst: 12%
- Others: 11%
- Chiron: 9%

*2003
World’s Firsts

- Rubella Vaccine: 1969
- Recombinant Hepatitis B Vaccine: 1986
- Thermostable Measles Vaccine: 1976
- Varicella Vaccine: 1984
- Combined Hepatitis A & B Vaccine: 1996
- Combined DTaP/Hib & DTaP IPV: 1997
- Combined Hepatitis A & Typhoid: 2000
- DTaP HBV IPV: 2000
- Combined Meningitis ACW135: 2003

Long History of Innovation
Contributions to World’s Health

• In 2004, nearly one and a half billion GSK vaccines distributed
  – Approximately 85% delivered to the developing world
  – Nearly three million doses each day

• Primary Supplier to International Health Organizations
  – UNICEF
  – WHO
  – PAHO

• GSK provides vaccines to developing world at affordable cost
  – Introduce new vaccines where most needed, not where most financially advantageous
Cervical Cancer – The Scope of the Problem

- Every two minutes a woman dies of cervical cancer worldwide
  - 10 women die every day in the U.S.
- All sexually active women are at risk of oncogenic HPV†
  - Includes women over age 25
- HPV-16 / 18 / 45 / 31 are responsible for ~80% of invasive cervical cancers worldwide°
- Adenocarcinoma of the cervix is increasing despite screening effortsX
  - HPV 16 / 18 / 45 / 31 responsible for 98% of cervical adenocarcinoma

Search for a Cervical Cancer Vaccine

• Safe
• Immunogenic
  – Strong immune response against oncogenic HPV
  – Provide high protective levels of antibody
• Broad protection against cervical cancer
  – Protect women from oncogenic HPV
  – Protect against the most common types
• Provide long lasting duration of protection
  – Sustained immune response
  – Long term protection
GSK’s HPV 16/18 Cervical Cancer Vaccine

• Novel GSK Adjuvant System
  • AS04 (Al + MPL®)
  • To enhance immune responses

• Vaccine composition
  • 20 µg HPV 16 L1 VLP
  • 20 µg HPV 18 L1 VLP
  • Administration schedule – 0, 1, 6 months
  • 50 µg MPL®
  • 500 µg AlOH₃

• Focus on cervical cancer prevention
  • Oncogenic HPV
  • Directed to women
  • Continuation of current cervical cancer screening methods
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- AS04
  - 50 µg MPL®
  - 500 µg AlOH₃
What is an Adjuvant?

- From Latin ‘adjuvare’: to help
- An adjuvant can be an immunostimulant and/or a carrier
  - carrier: a compound that transports the antigen: ALOH3
  - immunostimulant: a compound that acts directly or indirectly on the immuno competent cells to increase the immune response to a given antigen: MPL®
- It is designed to increase the specific immune response intensity, quality and breadth
Novel Adjuvant: Why AS04 for HPV?

• Prevention of HPV infection requires presence of neutralizing antibodies at the site of potential infection (cervix)
• High serum antibody concentrations that then transudate to the site of the infection
• AS04 versus traditional aluminum*
  – Higher and more persistent humoral antibody response
  – Higher frequency of memory B cells

* Giannini S et al. Vaccine 2006
AS04 versus Aluminum

Neutralizing Antibody

Time (months)

Enhanced and Sustained Immunogenicity Over 4 Years

* Statistically significant

Giannini SL et al. Vaccine 2006
Clinical Experience with AS04 Adjuvant

- AS04 used in several vaccines developed by GSK
  - Superiority of immune profile induced by AS04 vs alum formulations
  - 16,000 subjects received ~43,000 doses of AS04 in 40 completed and 4 ongoing studies
  - gD-AS04 (genital HSV vaccine)- Now in large-scale phase III trials including NIH collaboration
  - FENDrix™- adjuvanted HBsAg for use in hemodialysis patients; recently approved in EU (2005)
  - Generally well tolerated
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  - Oncogenic HPV
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AS04
HPV Types in Cervical Cancer

Cancer cases attributed to the most frequent HPV genotypes (%)

- HPV genotype 16: 53.5%
- HPV genotype 18: 70.7%
- HPV genotype 45: 77.4%
- HPV genotype 31: 80.3%
- HPV genotype 33: 2.6%
- HPV genotype 52: 2.3%
- HPV genotype 58: 2.2%
- HPV genotype 35: 1.4%
- HPV genotype 59: 1.3%
- HPV genotype 56: 1.2%
- HPV genotype 51: 1.0%
- HPV genotype 39: 0.7%
- HPV genotype 68: 0.6%
- HPV genotype 73: 0.5%
- HPV genotype 82: 0.3%
- Other: 1.2%
- X: 4.4%

HPV Types in Cervical Adenocarcinoma

HPV genotype

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Adenocarcinoma cases (%)</th>
<th>Vaccine types</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>52.1</td>
<td>52.1%</td>
</tr>
<tr>
<td>18</td>
<td>39.0</td>
<td>91.1%</td>
</tr>
<tr>
<td>45</td>
<td>6.2</td>
<td>97.3%</td>
</tr>
<tr>
<td>31</td>
<td>0.7</td>
<td>98.0%</td>
</tr>
</tbody>
</table>

Adenocarcinoma cases attributed to the listed HPV genotypes (%)

HPV – The Disease Burden in Women

• 90.3% of cancers attributable to oncogenic HPV occur solely in women
  – Cervix – 86.5%
  – Vulva / Vagina – 3.8%

• This does not include other sites of cancer attributable to oncogenic HPV
  – Anal
  – Oro-pharyngeal
  – Mouth

Clinical Trial Data
Study HPV 001

Vaccine efficacy (%)

Initial efficacy study (001) 001 / 007 combined analyses

Vaccine efficacy (%)

- Incident Infection
- 6M Persistent Infection
- 12M Persistent Infection post hoc analysis
- Cytology
- CIN

92% 100% 100% 93% 100%

Figure based on Harper et al. Lancet. 2004; 364: 1757
Study HPV 007

Vaccine efficacy (%)

HPV-16/18 associated

<table>
<thead>
<tr>
<th></th>
<th>Initial efficacy study (001)</th>
<th>001 / 007 combined analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident Infection</td>
<td>ATP 92%</td>
<td>ATP 97%</td>
</tr>
<tr>
<td>6M Persistent Infx</td>
<td>ATP 100%</td>
<td>ATP 94%</td>
</tr>
<tr>
<td>12M Persistent Infection post hoc analysis</td>
<td>ATP 100%</td>
<td>ATP 100%</td>
</tr>
<tr>
<td>Cytology</td>
<td>ITT 93%</td>
<td>ITT 96%</td>
</tr>
<tr>
<td>CIN</td>
<td>ITT 100%</td>
<td>ITT 100%</td>
</tr>
</tbody>
</table>

Figure based on Harper et al. Lancet. 2004; 364: 1757
Sustained Seropositivity and High Antibody Levels up to 4.5 Years

Figure based on Harper et al. Lancet. 2004; 364: 1757
Sustained Seropositivity and High Antibody Levels up to 4.5 Years

Figure based on Harper et al. Lancet. 2004; 364: 1757
**GSK studies 001 & 007 up to 4.5 years**  
First Evidence of Broader Protection

Independent of HPV DNA status

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Vaccine</th>
<th>Placebo</th>
<th>Vaccine efficacy (%) (95% CI)</th>
<th>p-values</th>
<th>Estimated prevalence of HPV-16/18</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>n</td>
<td>N</td>
<td>n</td>
<td></td>
</tr>
<tr>
<td>≥ASCUS</td>
<td>505</td>
<td>90</td>
<td>497</td>
<td>138</td>
<td>39.8 (20.9-54.4)</td>
</tr>
<tr>
<td>≥LSIL</td>
<td>505</td>
<td>41</td>
<td>497</td>
<td>70</td>
<td>44.6 (17.4-63.3)</td>
</tr>
<tr>
<td>CIN1+</td>
<td>481</td>
<td>12</td>
<td>470</td>
<td>24</td>
<td>51.5 (-0.9-77.9)</td>
</tr>
<tr>
<td>CIN2+</td>
<td>481</td>
<td>3</td>
<td>470</td>
<td>11</td>
<td>73.3 (-1.0-95.2)</td>
</tr>
</tbody>
</table>


GSK studies 001 & 007 up to 4.5 years
First evidence of cross protection types 45 & 31

Incident infection with most common oncogenic types beyond 16 & 18

<table>
<thead>
<tr>
<th>HPV Type</th>
<th>Vaccine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Event rate (rate per 100) (95% CI)</td>
<td>Event rate (rate per 100) (95% CI)</td>
</tr>
<tr>
<td></td>
<td>Rate</td>
<td>Rate</td>
</tr>
<tr>
<td>N</td>
<td>n</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>HPV-45</td>
<td>528</td>
<td>1</td>
</tr>
<tr>
<td>HPV-31</td>
<td>528</td>
<td>14</td>
</tr>
<tr>
<td>HPV-33</td>
<td>529</td>
<td>12</td>
</tr>
<tr>
<td>HPV-52</td>
<td>524</td>
<td>40</td>
</tr>
<tr>
<td>HPV-58</td>
<td>529</td>
<td>14</td>
</tr>
</tbody>
</table>

Study not powered to evaluate cross protection against all individual types

Combined initial efficacy and extended follow up studies
GSK studies HPV-001 & 007
Major findings

• Duration of protection
  – Sustained efficacy against HPV 16 / 18 infections and associated lesions for up to 4.5 years
  – Longest peer-reviewed efficacy follow up for any commercial formulation

• Sustained immune response
  – Persistent antibody levels in virtually 100% of patients over 4.5 years

• Broad oncogenic protection
  – Efficacy beyond 16/18 (broader protection) largely due to cross protection against HPV types 31 and 45

# GSK study HPV-007
## Safety Profile during Extended Follow Up

<table>
<thead>
<tr>
<th></th>
<th>Vaccine N (%)</th>
<th>Placebo N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women with at least one adverse event reported</td>
<td>54 (15.4%)</td>
<td>81 (23.5%)</td>
</tr>
<tr>
<td>Adverse events reported</td>
<td>65</td>
<td>98</td>
</tr>
<tr>
<td><strong>New Onset Chronic Disease (NOCD)</strong>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women with at least one NOCD event reported</td>
<td>10 (2.9%)</td>
<td>18 (5.2%)</td>
</tr>
<tr>
<td>NOCD events reported</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td><strong>Serious adverse events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women with at least one SAE reported</td>
<td>16 (4.6%)</td>
<td>19 (5.5%)</td>
</tr>
<tr>
<td>SAEs reported</td>
<td>21</td>
<td>19</td>
</tr>
</tbody>
</table>

*Including auto immune diseases


ATP Safety analysis
Age Bridging Trials

• **Pre-teen/adolescent girls**
  – HPV-012
    Immunological bridge 10-14 yrs and 15-25 yrs
    Safety/reactogenicity

• **Women >25 years**
  – HPV-014
    Immunological bridge 15-25 yrs and 26-55 yrs
    Safety
HPV-012 Results

- 100% of initially seronegative subjects seroconverted to both HPV-16 and HPV-18 positive
- GMTs in 10-14 yr olds >2-fold higher than 15-25 yr olds

Age Bridging Trials

- **Pre-teen/adolescent girls**
  - HPV-012
    Immunological bridge 10-14 yrs and 15-25 yrs
    Safety/reactogenicity

- **Women >25 years** (HPV-014)
  - HPV-014
    Immunological bridge 15-25 yrs and 26-55 yrs
    Safety
HPV-014 - Results

• Month 7
  – 100% of subjects were seropositive to both HPV-16 and HPV-18 with high GMTs at month 7
  – Age dependent decrease in GMTs but absolute values were high
HPV-16 Antibody Levels – Efficacy Study 001 / 007

HPV 16 Antibody Levels by Age Group

Study 014

HPV-16 GMC EU/ml

Month

0 7 12 18 33-38 45-50

Natural Infection

15 – 25 y.o.

Efficacy study

15-25y

Shwarz, T, et al. ASCO, 2006, Atlanta, USA
HPV 16 Antibody Levels by Age Group
Study 014

HPV-16 GMC EU/ml

<table>
<thead>
<tr>
<th>Month</th>
<th>Efficacy study</th>
<th>15-25y</th>
<th>26-35y</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td>55</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>18</td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>33-38</td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>45-50</td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Natural Infection
15 – 25 y.o.

Shwarz, T, et al. ASCO, 2006, Atlanta, USA
HPV 16 Antibody Levels by Age Group

Study 014

Shwarz, T, et al. ASCO, 2006, Atlanta, USA
Efficacy study

Natural Infection

15 – 25 y.o.

Shwarz, T, et al. ASCO, 2006, Atlanta, USA
HPV 18 Antibody Levels by Age Group
Study 014

Shwarz, T, et al. ASCO, 2006, Atlanta, USA
In all age groups, the vaccine was:

- Generally well tolerated
- Highly immunogenic:
  - **Seroconversion**: 100% for both antigens as early as the 2nd dose of vaccine
  - **Antibody levels**
    - at least 16-26 times higher than those associated with natural HPV infection
    - ≥ levels of antibodies associated with protection against HPV infection and its associated outcomes

Shwarz, T, et al. ASCO, 2006, Atlanta, USA
Safety profile in women 15-55 years of age

>95% study compliance

Shwarz, T, et al. ASCO, 2006, Atlanta, USA
## Phase III Efficacy Program

<table>
<thead>
<tr>
<th>GSK efficacy study (HPV 008)</th>
<th>NCI supportive study (HPV 009)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Double blind, randomised, controlled</td>
<td>Double blind, randomised, controlled</td>
</tr>
<tr>
<td>Multi-centre (90+)</td>
<td>Population-based</td>
</tr>
<tr>
<td>Multi-country (14)</td>
<td>&gt; 6 centres in Costa Rica</td>
</tr>
<tr>
<td>18,665 women aged 15–25 years</td>
<td>7465 women aged 18–25 years</td>
</tr>
<tr>
<td>CIN II+</td>
<td>CIN II+</td>
</tr>
</tbody>
</table>
GSK HPV 16/18 Vaccine
Global Clinical Development Plan
<table>
<thead>
<tr>
<th>Year</th>
<th>Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>HPV-007 Efficacy Y1*</td>
</tr>
<tr>
<td>2006</td>
<td>HPV-012 (immuno 10-25y) LT follow-up</td>
</tr>
<tr>
<td>2007</td>
<td>HPV-013 (adol. safety) LT follow-up</td>
</tr>
<tr>
<td>2008</td>
<td>HPV-014 (immuno 15-55y) LT follow-up</td>
</tr>
<tr>
<td>2009</td>
<td>HPV-008: CIN2+ efficacy-global (N = 18,668) Long term immunogenicity HPV-009: CIN2+ efficacy-Costa Rica (N = 7,467)</td>
</tr>
</tbody>
</table>

>30,000 subjects enrolled in ongoing trials

*4 yrs of follow-up
Conclusions

• GSK’s commitment to those in need
  – Worldwide and the U.S.

• Search for a cervical cancer vaccine
  – Novel adjuvant – AS04
    • Stronger immune response compared to our vaccine formulated with Al adjuvant
  – Focused on cervical cancer
    • HPV 16 / 18
  – Directed to women
Conclusions (Cont’d)

• Safety profile
  – Well tolerated in clinical trials

• Immunogenic
  – No evidence of waning immunity to HPV 16 / 18 through 4.5 years

• Broad protection against oncogenic HPV
  – Efficacy beyond HPV 16 and 18 due to protection against HPV types 45 and 31

• Long duration of protection
  – Sustained efficacy against HPV 16 and 18 for up to 4.5 years
  – Persistent antibody levels in nearly 100% of patients