Experience with GSK’s H5N1 and H1N1 Influenza Vaccine

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Outline

- Overview of clinical/preclinical data of GSK’s AS03$_A$-adjuvanted H5N1 vaccine

- Flexible prime-boost vaccination strategy using GSK’s AS03$_A$-adjuvanted H5N1 vaccine

- Safety

- Real life demonstration of high vaccine effectiveness of GSK’s AS03$_A$-adjuvanted pandemic H1N1 influenza in all age groups – Canada and Germany
GSK’s $\text{AS03}_A$-Adjuvanted H5N1 Influenza Vaccine Has Received Market Authorisation

- Europe
- Switzerland
- Norway
- Iceland
- Singapore
- Hong Kong
- Malaysia
- South Korea

**Therapeutic indications**

- Active immunization against H5N1 subtype of influenza A virus
- Indication is based on immunogenicity data from healthy subjects aged 18–60 years following administration of two doses of vaccine prepared from A/Indonesia/05/2005 PR8-IBCDC-RG2 (H5N1)
- GSK’s $\text{AS03}_A$-adjuvanted H5N1 influenza vaccine should be used in accordance with official guidance
The AS03 Adjuvant System is Designed to Produce a Highly Targeted Immune Response

The AS03 Adjuvant System is a vitamin E-based, oil-in-water emulsion

<table>
<thead>
<tr>
<th>Component</th>
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</thead>
<tbody>
<tr>
<td>DL-α-tocopherol</td>
</tr>
<tr>
<td>Squalene</td>
</tr>
<tr>
<td>Polysorbate 80 (Tween™ 80)</td>
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</tbody>
</table>

# GSK’s AS03<sub>A</sub>-Adjuvanted H5N1 Influenza Vaccine Displays Several of the Essential Characteristics for a Prepandemic Influenza Vaccine

<table>
<thead>
<tr>
<th>Essential characteristics</th>
<th>Available data for GSK’s AS03&lt;sub&gt;A&lt;/sub&gt;-adjuvanted H5N1 influenza vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Be available before the onset of a pandemic and produced and stockpiled in advance</td>
<td>GSK’s AS03&lt;sub&gt;A&lt;/sub&gt;-adjuvanted H5N1 influenza vaccine is available and is licensed in several countries</td>
</tr>
</tbody>
</table>
| Have a favourable safety profile                                                          | Rumke et al. Vaccine 2008  
Chu et al. Vaccine 2009  
Diez-Domingo et al. Ped Inf Dis J 2010 |
| Immunogenic at low antigen content, 3.75 µg in adults (1.9 µg in children)                | Leroux-Roels et al. Lancet 2007  
Baras et al. PlosOne 2008  
Diez-Domingo et al. Ped Inf Dis J 2010 |
| Induce a broad, cross-clade immune response (human and ferrets) and protection (ferrets) against drifted strains | Leroux-Roels et al. Lancet 2007  
Leroux-Roels et al. PlosOne 2008  
Baras et al. PlosOne 2008 |
| Be produced on a large scale                                                              | Chu et al. Vaccine 2009 |
| Have flexibility of the interval between doses                                            | Leroux-Roels et al. Vaccine 2010 |
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Immunogenicity of GSK’s AS03$_A$-Adjuvanted H5N1 Influenza Vaccine in the Adult Population
GSK’s AS03ₐ-Adjuvanted H5N1 Influenza Vaccine Meets All Three CHMP Criteria in Adults at a Very Low Antigen Dose of 3.75 μg Per Dose

Cross Clade Immunity Studied
Persistence of Cross-Reactive Neutralizing Antibodies Demonstrated

Vaccinated with 2 doses 3.75 µg H5N1 A/Vietnam/1194/04 influenza vaccine

**NT Seroconversion rate**

- Persistent cross-neutralizing antibodies with high seroconversion rate at month 6 (40% clade 2.1, 70% clade 2.2 and 60% clade 2.3).
- No cross-reactive neutralising antibodies seen with non-adjuvanted vaccine.

The Ferret Model

A surrogate for clinical testing with live potentially pandemic influenza virus:

• Homologous challenge (A/Vietnam/1194/04)

• Heterologous challenge (A/Indonesia/5/05)
# Survival against Lethal H5N1 Challenge in Animal (Ferret) Model

<table>
<thead>
<tr>
<th>Study start</th>
<th>Day 0 Vaccination 1</th>
<th>Day 21 Vaccination 2</th>
<th>Day 49 Lethal Challenge</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A/Vietnam/1194/04</td>
<td>A/Vietnam/1194/04</td>
<td>A/Vietnam/1194/04 or A/Indonesia/5/05</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>Survival Homologous challenge&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Survival Heterologous challenge&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls*</td>
<td>1/11 (9%)</td>
<td>0/12 (0%)</td>
</tr>
<tr>
<td>H5N1 Vaccine – AS</td>
<td>6/6 (100%) (5µg H5N1-AS03)</td>
<td>6/6 (100%) (3.75µg H5N1-AS03)</td>
</tr>
<tr>
<td></td>
<td>4/5 (80%) (1.7µg H5N1-AS03)</td>
<td>5/6 (83%) (1.7µg H5N1-AS03)</td>
</tr>
</tbody>
</table>

<sup>1</sup> Benoît Baras et al. Abstract for Options for the Control of Influenza VI June 17–23, 2007 - Toronto, Canada

<sup>2</sup> Benoit Baras et al. Cross-protection against Lethal H5N1 Challenge in Ferrets with an Adjuvanted Pandemic Influenza Vaccine. PLOS one January 2008, Issue 1, e1401.

*Control in homologous study = saline OR adjuvant only
Control in heterologous study = antigen OR adjuvant only
Safety and Immunogenicity of GSK’s AS03$_A$-adjuvanted H5N1 Influenza Vaccine in the Asian Population
Study Sites for Phase III Study in a Large Population of Asian Adults (H5N1-002)

THAILAND
Siriraj Hospital

SINGAPORE
Changi General Hospital
National Healthcare Group Polyclinics- Choa Chu Kang

TAIWAN
National Taiwan University Hospital
Taipei Veterans General Hospital

HONG KONG
Queen Mary Hospital Sai Ying Pun Jockey Club
General Outpatient Clinic University of Hong Kong


NCT 00449670
Study Design for Phase III Study in a Large Population of Asian Adults

**Study population**
- 1206 healthy adult volunteers; 18-60 years old (mean age: 33.6 yrs)

**Objectives**
- To evaluate the safety of the AS adjuvanted formulation containing 3.75 μg H5N1 haemagglutinin
- To evaluate the immune response against clade 1 and clade 2 strains

**Vaccine composition**
- split virion prepandemic influenza candidate vaccine (A/Vietnam/1194/04)

**Study design**
- 2 vaccine doses administered 21 days apart
- 3.75 μg H5N1 haemagglutinin with (N=961) or without (N=245) AS adjuvant system
- 2 lots of HA antigen & 2 lots of AS adjuvant system tested

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**Study start**
- Day 0
  - Vaccination 1
  - Blood sample
- Day 7
  - Safety evaluation
- Day 21
  - Vaccination 2
  - Blood sample
- Day 28
  - Safety evaluation
- Day 42
  - Blood sample
Cross-Reactive Immunity of GSK’s AS03ₐ-Adjuvanted H5N1 Vaccine in the Asian Population

**Seroprotection rate (%)**

- A/Vietnam/1194/04 (Homologous strain)
- A/Indonesia/05/05 (Heterologous strain)

**Seroconversion rate (%)**

- A/Vietnam/1194/04 (Homologous strain)
- A/Indonesia/05/05 (Heterologous strain)

**Seroconversion Factor**

- D0
- D21
- D42

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**CHMP criteria**

Neutralizing Antibody Seroconversion Rates in Europe and Asia–Day 42

**Study H5N1-007 (Europe)**

- A/Vietnam/1194/04 (Homologous strain)
- A/Indonesia/05/05 (Heterologous strain)

**Study H5N1-002 (Asia)**

- A/Vietnam/1194/04 (Homologous strain)
- A/Indonesia/05/05 (Heterologous strain)

A marked heterologous immune response was demonstrated for neutralising antibody.

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GSK’s AS03$_A$-Adjuvanted H5N1 Vaccine Allows for a Highly Flexible Prime-Boost Vaccination Strategy (H5N1-012): Homologous Booster

Schwarz et al. Single dose vaccination with AS03-adjuvanted H5N1 vaccines in a randomized trial induces strong and broad immune responsiveness to booster vaccination in adults. Vaccine 2009; 27: 6284-6290.
Schwarz et al. Single dose vaccination with AS03-adjuvanted H5N1 vaccines in a randomized trial induces strong and broad immune responsiveness to booster vaccination in adults. Vaccine 2009; 27: 6284-6290.
Results – GMTS against A/Vietnam

Schwarz et al. Single dose vaccination with AS03-adjuvanted H5N1 vaccines in a randomized trial induces strong and broad immune responsiveness to booster vaccination in adults. Vaccine 2009; 27: 6284-6290.
GSK’s AS03\textsubscript{A}-Adjuvanted H5N1 Vaccine and the Highly Flexible Prime-Boost Vaccination Strategy (H5N1-012)

- Regardless of the primary vaccination schedule, 1-dose booster vaccination induced a high immune response.

- Similar GMT levels were reached 21 days after the 2-dose primary vaccination and 21 days after booster vaccination.

Schwarz et al. Single dose vaccination with AS03-adjuvanted H5N1 vaccines in a randomized trial induces strong and broad immune responsiveness to booster vaccination in adults. Vaccine 2009; 27: 6284-6290.
GSK’s AS03_A-Adjuvanted H5N1 Vaccine and the Highly Flexible Prime-Boost Vaccination Strategy (H5N1-012): Heterologous Booster

Schwarz et al. Single dose vaccination with AS03-adjuvanted H5N1 vaccines in a randomized trial induces strong and broad immune responsiveness to booster vaccination in adults. Vaccine 2009; 27: 6284-6290.
GSK’s AS03<sub>A</sub>-Adjuvanted H5N1 Vaccine and the Highly Flexible Prime-Boost Vaccination Strategy: Heterologous Booster

Results – Seroprotection Rate after Primary Vaccination

Schwarz et al. Single dose vaccination with AS03-adjuvanted H5N1 vaccines in a randomized trial induces strong and broad immune responsiveness to booster vaccination in adults. Vaccine 2009; 27: 6284-6290.
Using Combination of Different H5N1 Vaccine Strain gives Good Immunogenicity for Both Strains

Results – Post-boosting Seroprotection Rate

Schwarz et al. Single dose vaccination with AS03-adjuvanted H5N1 vaccines in a randomized trial induces strong and broad immune responsiveness to booster vaccination in adults. Vaccine 2009; 27: 6284-6290.
Vaccination Strategy Using a Combination of Vietnam and Indonesia Strains

**Single dose priming at day 0**
- Dose 1 VT

**Boosting at mth 6 or mth 12**
- Dose 2 VT
- Dose 2 IN

**2-dose priming at day 0 & 21**
- Dose 1 VT
- Dose 2 VT

**Boosting at mth 6 or mth 12**
- Dose 3 VT
- Dose 3 IN

**VV12** (n=55)  
**VI12** (n=53)
2 Doses Primary Vaccination Given 12 mths Apart: Induced Rapid and Strong Cross-Clade Immune Response

Tino Schwarz et al_Abstract presented at IVW, Cannes, France, 27–30 April 2009
Adults vaccinated with 2 doses 3.75 µg AS03-adjuvanted H5N1 A/Indonesia/5/2005 prepandemic vaccine
Conclusion and Practical Implications

- Administration flexibility: adaptable to local prepandemic vaccination policies
- Stockpiles of GSK AS03-adjuvanted vaccines derived from different H5N1 strains may be compatible with each other
- Potential for reducing the logistic stress on vaccination programme delivery during the crucial first months of pandemic

GSK’s AS03$_A$-adjuvanted H5N1 vaccine is a step forward in the prevention of possible H5N1 pandemics and has the potential to reduce the overall burden of disease in countries where both H5N1 and H1N1 influenza virus strains are epidemic.

Schwarz et al. Single dose vaccination with AS03-adjuvanted H5N1 vaccines in a randomized trial induces strong and broad immune responsiveness to booster vaccination in adults. Vaccine 2009; 27: 6284-6290.
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Safety Demonstrated in Studies in Asia & Europe

Safety Data:
- Safety study of 5071 adults using 15 µg H5N1 + AS vaccine, compared to seasonal flu + placebo
- Overall, large clinical trials in over 6700 subjects (both adults and children aged 3–9 yrs) vaccinated

Key Conclusions:
- Higher incidence of local and general symptoms in adjuvanted group vs non-adjuvanted vaccine
- Overall reactogenicity profile was clinically acceptable with no safety concerns
- Most symptoms were mild or moderate and transient (mostly resolved within 3 days)
- No serious adverse events were reported

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GSK is Using the Twin-Vial Antigen-Adjuvant Vaccine, Permitting Flexible Supply

Add AS03 to antigen, shake well

Withdraw 1 dose (0.5 ml) to administer (I.M.)
Comparing GSK’s AS03<sub>A</sub>-Adjuvanted Vaccines—H5N1 versus H1N1

Seroprotection Rate

Seroconversion Rate

Seroconversion Factor

CHMP criterion

H1N1 Clinical Studies

- GSK’s adjuvanted H1N1 vaccines are very immunogenic in all populations including the elderly and very young
- GSK’s adjuvanted H1N1 vaccines showed an acceptable safety profile in all populations
- GSK’s adjuvanted vaccines from the two manufacturing sites are clinically equivalent
GSK Pandemic H1N1 Vaccine Clinical Data

Seroprotection Rate

Seroconversion Rate

Seroconversion Factor

--- CHMP Criteria for adults (aged 18–60yrs)
--- CHMP Criteria for elderly (aged >60yrs)
Canada: Effectiveness of GSK’s AS03-Adjuvanted Pandemic H1N1 2009 Vaccine

Community based case-control vaccine effectiveness review of children < 10 years with influenza-like illness who were tested for H1N1 infection at the central provincial laboratory.

- Children 36 months to <10 years
  - Well: received a single dose of 0.25 ml of GSK’s AS03-adjuvanted pandemic H1N1 vaccine (1.9 μ g HA).
  - Chronic medical conditions: received 2 doses, 21 days apart.

- Children 6 months to 35 months received two doses, 21 days apart.

Canada: Effectiveness of GSK’s AS03-Adjuvanted Pandemic H1N1 2009 Vaccine

Number of positive pandemic influenza specimens and percent of immunized children 6 months to 9 years with H1N1 vaccine, New Brunswick

Canada: Effectiveness of GSK’s AS03-Adjuvanted Pandemic H1N1 2009 Vaccine

Conclusion

As stated by Van Buynder PG et al.

(New Brunswick Department of Health, Office of the Chief Medical Officer of Health, New Brunswick, Canada):

“If vaccination was designated to be effective after 14 days, none of the vaccinated child had laboratory confirmed influenza as compared to 38% of controls. The vaccine effectiveness of 100% was statistically significant for children <10 years and <5 years of age considered separately.

If vaccination was considered effective after 10 days, vaccine effectiveness dropped to 96% overall, but was statistically significant and over 90% in all age subgroups, including <36 months.”

Germany: Effectiveness of GSK’s AS03-Adjuvanted Pandemic H1N1 2009 Vaccine

71315 laboratory confirmed H1N1 cases
45733 cases with available information
425 cases were vaccinated
289 cases with disease onset data

Germany: Effectiveness of GSK’s AS03-Adjuvanted Pandemic H1N1 2009 Vaccine

289 H1N1 cases with complete data:
- 228 cases were vaccinated < 14 days before onset of symptoms
- 61 cases were vaccinated > 14 days before onset of symptoms

Germany: Effectiveness of GSK’s AS03-Adjuvanted Pandemic H1N1 2009 Vaccine

<table>
<thead>
<tr>
<th>Age</th>
<th>H1N1 cases</th>
<th>H1N1 cases with vaccination status</th>
<th>Vaccine failures A</th>
<th>Expansion factor B</th>
<th>Vaccine failures C</th>
<th>Proportion H1N1 cases D</th>
<th>Proportion vaccinated (95% CI) E</th>
<th>VE (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Not vaccinated</td>
<td>vaccinated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14-59 y</td>
<td>37 756</td>
<td>23 853</td>
<td>219</td>
<td>35</td>
<td>1.52 (219/144)</td>
<td>53.2</td>
<td>0.0022 (0.044-0.093)</td>
<td>96.8% (95.2-97.9)</td>
</tr>
<tr>
<td>≥ 60 y</td>
<td>430</td>
<td>923</td>
<td>25</td>
<td>7</td>
<td>1.92 (25/13)</td>
<td>13.4</td>
<td>0.0141 (0.047-0.131)</td>
<td>83.3% (71.0-90.5)</td>
</tr>
</tbody>
</table>

A: Cases with disease >14 days after vaccination
B: (Total vaccinated cases/vaccinated cases with information on date of vaccination and symptom onset)
C: After applying expansion factors
D: With vaccine failure among H1N1 cases with available vaccination status
E: In the general population

Conclusion

As stated by Wichmann O et al. (Robert Koch Institute, Berlin, Germany):

- “Excellent VE in persons 14 to 59 years: 96.8% (95% CI 95.2-97.9)”
- “Moderately high VE in persons ≥60 years: 83.3% (95% CI: 71-90.5)”

Thank You