A Human Rotavirus Vaccine

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Rotarix is a trade mark of the GlaxoSmithKline group of companies
Biography of a Human Attenuated RV Vaccine Rix4414

89-12 strain isolated from stools of a 15-month old boy in Cincinnati

Passaged in Primary African Green Monkey Kidney (AGMK)

Further Passaged in AGMK

Further Passaged in Vero Cell Line & Cloning steps

Further passaged in Vero cell line

RIX4414 master seed

AVANT Immunotherapeutics

J Gamble Inst. Med. Research, Cincinnati

GSK Bio

Rotarix™ vaccine lot
Why was HRV strain 89-12 a good vaccine candidate?

- 1989: Natural infection with 89-12 G1 RV strain from Cincinnati provided excellent protection against RV disease during next RV season

- Live vaccine was prepared by serial passage of 89-12 strain

- 1997-98: Placebo controlled study reported a VE against “any” RV GE of 89% and 100% against “very severe” RVGE

- 1998-99: F/U showed protection in a 2nd year of 100% against “very severe” RVGE

Vaccine Profile

• Live, attenuated, human RV (parent strain 89-12)\(^1\)

• G1P[8]\(^2\)

• Broad cross-protection\(^2,3\)

• Oral, 1mL

• Two doses from 6 weeks of age, minimum 4 weeks apart\(^4\)

• Storage at 2–8°C \(^4\)

• Co-administration with other vaccines: DTPw, DTPa, HBV, Hib, IPV, OPV \(^4\), Men C \(^5\), Strep pneum\(^6\)

Phase I – II – III Studies

... a worldwide development
Phase III Efficacy and Safety Study 023
Latin-America & Finland
Phase III study in Latin America (023)

Trial profile

Routine immunizations were co-administered according to local regulations

Study conducted in 4Q 2003-2005 (2yr)

Safety cohort (N=63,225) 18 sites in 12 countries

- Mexico: 13245 (20.9%)
- Dominican Republic: 4056 (6.4%)
- Panama: 4061 (6.4%)
- Venezuela: 4250 (6.7%)
- Brazil: 3218 (5.1%)
- Colombia: 3910 (6.2%)
- Peru: 12044 (19.0%)
- Argentina: 4671 (7.4%)
- Finland: 2060 (3.3%)
- Honduras: 4195 (6.6%)
- Nicaragua: 4057 (6.4%)
- Chile: 3458 (5.5%)
Methods

Placebo-controlled, randomized, double blind study (N=63,225)

• Study population
  31.673 vaccinees and 31.552 placebo recipients
  • Dose 1: mean age 8.2 weeks (97% ≤ 13 weeks old)
  • Dose 2: mean age 15.8 weeks

• Case Definition
  Definite IS according to Brighton Collaboration Group
  • Demonstration at surgery
  • Gas or liquid contrast enema
  • Abdominal ultrasound with specific characteristic features proven to be reduced by hydrostatic enema
  • Autopsy criteria

Pivotal Phase III Study 023 – Safety

Occurrence of Definite IS Cases Compared to RotaShield™-Associated Cases¹

Dose 1

IS cases

Dose 2

IS cases

V = Vaccine  P = Placebo

Safety - Intussusception Surveillance

**Vaccine group**
- Safety cohort N=31,673
- Efficacy cohort N=10,159

**Placebo group**
- Safety cohort N=31,552
- Efficacy cohort N=10,010

Cases of IS
- 0 → 31 days
  - Vaccine group: 6 cases
  - Placebo group: 7 cases
  - Relative Risk = 0.85 (0.30; 2.42)

- 0 → 100 days
  - Vaccine group: 9 cases
  - Placebo group: 16 cases
  - Relative Risk = 0.56 (0.25; 1.24)
  - Relative Risk = 0.1 (0.02; 0.60)

- 0 → 1 year
  - Vaccine group: 4 cases
  - Placebo group: 14 cases
  - Relative Risk = 0.28 (0.1; 0.81)

References:
- Macias, abstract, ICAAC, 2005, Washington, USA (poster)
Study 023 – Latin America
Results: 1yr Efficacy
Vaccine efficacy against severe RV GE

From 2 weeks post-dose 2 to 1 year of age

<table>
<thead>
<tr>
<th></th>
<th>N subjects with severe RV GE</th>
<th>Vaccine efficacy (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vaccinees</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=9,009</td>
<td>12</td>
<td>84.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>(71.7 - 92.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=8,858</td>
<td>77</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vesikari score ≥11</strong></td>
<td></td>
<td>84.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>(71.1 – 92.7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ATP efficacy cohort

Vaccine efficacy against RV GE hospitalization

From 2 weeks post-dose 2 to 1 year of age

<table>
<thead>
<tr>
<th></th>
<th>Vaccinees n=9,009</th>
<th>Placebo n=8,858</th>
<th>Vaccine efficacy [95% CI]</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>9</td>
<td>59</td>
<td>85 (69.6 - 93.5)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Vaccine Efficacy against any GE hospitalization 42% (95% CI 29-53)

**Pivotal Phase III Study 023 – Efficacy**

Efficacy against severe RV GE by main serotype

From 2 weeks post-dose 2 to 1 year of age (95% CI)

- **G1P[8]**: 91.8% (74.1 - 98.4)
- **G3P[8], G4P[8], G9P[8]**: 87.3% (64.1 - 96.7)
- **G2P[4]**: 86.9% (62.8 - 96.6)

ATP efficacy cohort

- Clinical: 45.4% (-81.5 - 85.6)
- Vesikari scale: 41.0% (-79.2 - 82.4)

\* In a meta-analysis including the results of 023 and 2 phase II studies, the efficacy of RIX4414 against the G2P[4] type was **67% (CI 95%: 15 - 87%)**

Effect On Co-administered Vaccines

Sero-positivity / protection rate of DTPw-HBV/Hib and OPV separately (post dose 2)

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>RIX4414</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>100</td>
<td>90</td>
</tr>
<tr>
<td>T</td>
<td>100</td>
<td>90</td>
</tr>
<tr>
<td>Pertussis</td>
<td>60</td>
<td>70</td>
</tr>
<tr>
<td>HBV</td>
<td>100</td>
<td>90</td>
</tr>
<tr>
<td>Hib (PRP)</td>
<td>100</td>
<td>90</td>
</tr>
<tr>
<td>Polio 1</td>
<td>100</td>
<td>90</td>
</tr>
<tr>
<td>Polio 2</td>
<td>100</td>
<td>90</td>
</tr>
<tr>
<td>Polio 3</td>
<td>60</td>
<td>70</td>
</tr>
</tbody>
</table>

1 ELISA, cut off at 0.1UI/mL  
2 ELISA, cut off at 15 EL.U/mL  
3 AUSAB, Abbott Laboratories cut off at 10mIU/mL  
4 ELISA, cut off at 0.15 µg/mL  
5 Virus microneutralization cut off titer ≥8

Effect On Polio 1, 2 & 3 Seroprotection After D3

- **Polio 1**: Study 014, Study 013, Study 024
- **Polio 2**: Study 014, Study 013, Study 024
- **Polio 3**: Study 014, Study 013, Study 024

Virus microneutralization cut off titer $\geq 8$

(RIX4414 + IPV, RIX4414 + OPV, Placebo + OPV)
Phase III Efficacy Study 036
Europe
Phase III Study in Europe (036)

Trial profile

n=3,994 infants enrolled and randomised (2:1)

n=2,646

1st dose

Month 0
Age 6-14 weeks

n=1,348

2nd dose

Months 1–2
Age 10–24 weeks

RIX4414

Placebo

months

Months 7-9
Age 10-11 months

Season 1 efficacy analysis

Months 19-21
Age 22-23 months

Season 2 efficacy analysis

Co-administered with routine childhood vaccinations

Study conducted 4Q 2004 – 2005 (Yr 1)

Vesikari T et al. ESPID, Basel, Switzerland May 3–5, 2006, Abstract 75
Phase III Study 036 - Objectives

124 sites in 6 EU countries ~4000 infants
Study Design

- Randomized, double-blind, placebo-controlled study in 6 European countries
  - 2646 vaccinees
  - 1348 placebo recipients
- Dose 1: 5-18 weeks of age (mean: 11.5 wks)
- Dose 2: 10-30 weeks of age (mean: 19.6 wks)
- Co-administration with routine childhood vaccines
- Surveillance period: 6 months, until end of the 1st RV season after vaccination (second year ongoing)
- ~ 90% of infants not vaccinated before RV season
- Peak incidence of RVGE April - May 2005
Methods

- **Gastroenteritis**: Diarrhea with or without vomiting
- **Severe GE**: Score $\geq 11$ on 20-point Vesikari scale\textsuperscript{1}
- **GE Stools analyzed** for RV by ELISA (*RotaClone*\textsuperscript{TM}). RV positive samples tested by RT-PCR followed by Reverse Hybridization assay to determine G and P types
  - Primary analysis on ATP cohort including 2572 vaccinees and 1302 placebo recipients

\textsuperscript{1} Ruuska and Vesikari, Scand J Infect Dis, 1990
**Routine vaccines co-administered according to national immunisation schedules**

**Age of vaccine administration (months)**

<table>
<thead>
<tr>
<th>Country</th>
<th>\textit{Infanrix hexa}™ (DTPa, HBV, IPV, Hib vaccine, GSK)</th>
<th>\textit{Infanrix™ Polio Hib} (DTPa, IPV, Hib vaccine, GSK)</th>
<th>Meningococcal group C conjugate vaccine, Wyeth</th>
<th>Pneumococcal polysaccharide conjugate vaccine 7-valent, Wyeth</th>
<th>\textit{Rotarix}™</th>
</tr>
</thead>
<tbody>
<tr>
<td>Czech Republic</td>
<td>3,4,5</td>
<td></td>
<td></td>
<td></td>
<td>3,4</td>
</tr>
<tr>
<td>Finland</td>
<td>3,5,11-12</td>
<td></td>
<td></td>
<td></td>
<td>3,5</td>
</tr>
<tr>
<td>France</td>
<td>2,4</td>
<td>3</td>
<td></td>
<td>2,3,4</td>
<td>2,3</td>
</tr>
<tr>
<td>Germany</td>
<td>2,3,4</td>
<td></td>
<td></td>
<td>2,3,4</td>
<td>2,3</td>
</tr>
<tr>
<td>Italy</td>
<td>3,5,11</td>
<td></td>
<td></td>
<td></td>
<td>3,5</td>
</tr>
<tr>
<td>Spain</td>
<td>2,4,6</td>
<td>2,4,6</td>
<td></td>
<td>*</td>
<td>2,4</td>
</tr>
</tbody>
</table>

* 7vPCV administered intermittently at 3, 5 and 7 months

DTPa: diphtheria and tetanus toxoids and acellular pertussis; HBV: hepatitis B virus; Hib: \textit{Haemophilus influenzae} type B; IPV: inactivated poliovirus

Study 036 – Europe
Results: 1yr Efficacy
Vaccine efficacy against RVGE episodes

From 2 weeks post-dose 2 to end of the 1st RV season (ATP cohort) (CI 95%)

- Any RVGE: 87% [80;92]
- Severe RVGE: 96% [90;99]
- RVGE hospitalizations: 100% [82;100]

Vesikari T et al. ESPID, Basel, Switzerland May 3-5, 2006 Abstract 75
Serotype specific efficacy against severe RVGE

From 2 weeks post-dose 2 to end of the 1st RV season (ATP cohort) (95% CI)

- G1: 96% [86;100]
- G3: 100% [45;100]
- G4: 100% [65;100]
- G9: 95% [78;99]
- G2P[4]: 75%* [-386;100]

* Non statistically significant

Vesikari T et al. ESPID, Basel, Switzerland May 3-5, 2006 Abstract 75
**Efficacy against hospitalized GE due to any cause**

From 2 weeks post-dose 2 to end of the 1st RV season (ATP cohort)

<table>
<thead>
<tr>
<th></th>
<th>Vaccine</th>
<th>Placebo</th>
<th>Vaccine efficacy [95% CI]</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization for GE</td>
<td>11</td>
<td>22</td>
<td>75 [45; 89]</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Vesikari T et al. ESPID, Basel, Switzerland May 3-5, 2006 Abstract 75
Study 036 – Europe
Results: Immunogenicity and Co-administration
Co-administration – 
Rotarix™ and Infanrix™ combinations

Infanrix™ combination vaccines – antibody responses

- Similar between vaccinees and placebo recipients

- Seroprotection / seropositivity rates varied between
  - 92–99% in vaccinees
  - 91–100% in placebo recipients

Vesikari T et al. ESPID, Basel, Switzerland May 3–5, 2006, Abstract 458
### SBA-MenC antibody responses

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Seropositivity(†)% (95% CI)</th>
<th>GMT U/mL (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotarix™</td>
<td>184</td>
<td>100 (98-100)</td>
<td>1455 (1240-1708)</td>
</tr>
<tr>
<td>Placebo</td>
<td>90</td>
<td>100 (96-100)</td>
<td>1769 (1374-2278)</td>
</tr>
</tbody>
</table>

\(†\)SBA-MenC cut-off \(\geq\) 1/8 dilution

### Anti-PSC antibody responses

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Seropositivity(‡)% (95% CI)</th>
<th>GMC mcg/mL (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotarix™</td>
<td>187</td>
<td>100 (98-100)</td>
<td>8 (7-9)</td>
</tr>
<tr>
<td>Placebo</td>
<td>91</td>
<td>100 (96-100)</td>
<td>9 (8-10)</td>
</tr>
</tbody>
</table>

\(‡\)Men C anti-PSC cut-off \(\geq\) 0.3 μg/mL ELISA
Anti-pneumococcal antibody responses

• Varied by serotype and were between 89–100% (1 month post-dose 3)

• No difference in seropositivity between vaccinees and placebo recipients
Conclusions (1/2)

Two doses of Rotarix™, co-administered with specific childhood vaccines, significantly:

- Reduce severe RVGE disease (85% - 96%)
- Reduce any RVGE disease (87%)
- Reduce RVGE-related hospitalisations (85% - 100%)
- Protect against circulating wild-type G1, G3, G4 and G9 rotavirus strains
  - Protective trend against G2P[4]
- Reduce GE-related hospitalisations due to any cause (rotavirus or not) (42% - 75%)
Conclusions (2/2)

Rotarix™ and co-administered childhood vaccines

- High Rotarix™ immune responses maintained
- No impairment of immune responses to any co-administered vaccine antigens
- Rotarix™ can be recommended for incorporation into childhood immunisation schedules
  - 2, 3 months; 2, 4 months; 3, 4 months or 3, 5 months of age
- More data to come:
  - Efficacy and Safety in Asia and Africa
  - Safety in HIV positive infants
  - Transmission in twins
  - Immuno in pre-term infants
  - Immuno for Vaccine heat stability
  - Long term efficacy (2-3yr) in Latin-America / Eu / Asia ….
Licensed in 25 countries in Europe and in 41 other countries worldwide

Next registrations
- Applications submitted in >60 countries
- Further approvals expected during 2006 in
  - Latin America
  - Middle East
  - Africa
  - Asia Pacific Region

Universal Mass Vaccination
- Venezuela
- Panama
- Brazil
- Mexico (poorest provinces)
Evidence-based clinical practice guidelines on rotavirus vaccination in Europe
Progress To Date

"Guidelines for the prevention of Rotavirus disease in Europe: Expert Group Recommendations for Vaccination"

- Draft guidelines developed by an expert group
  - specializing in epidemiology, paediatrics, infectious diseases and public health
- To be endorsed by European Paediatric Societies - ESPID and ESPGHAN
- Publication of recommendations – planned for Q406
Thank you on behalf of millions of babies ….