Vi-CRM$_{197}$ conjugate vaccine against typhoid fever: development and early clinical testing

Audino Podda, Head of Clinical Development & Regulatory Affairs for the NVGH Development Project Team & Clinical Teams of the Vi-CRM$_{197}$ studies

8$^{th}$ International Typhoid Fever and Invasive Salmonelloses – Dhaka, Bangladesh
Agenda

- Status of project as presented in Kilifi
- Clinical plan overview
- Phase 1 & dose ranging studies
- Phase 2 studies in endemic countries
- Proposed basis for pre-qualification
- Next steps
- Acknowledgements
Vi-CRM$_{197}$: Laboratory proof of concept presented in Kilifi (Laura Martin | January 2009)

- Immunogenic and well tolerated
  - Antibody response is dose dependent
  - 1:1 or 2:1 weight ratio Vi:CRM$_{197}$ superior to 10:1 ratio

- anti-Vi antibody levels comparable to other Vi-conjugates
  - Analysis of sera supplied by NIH
  - Using CRM$_{197}$, TT conjugates made with Vi obtained from NIH
Vi-CRM$_{197}$ – Clinical development overview

A 30 month journey: key milestones

- **Feb 2010:** GMP lot released
- **Oct 2010:** Phase 2 started in EU
- **Sept 2011:** First clinical Paper published
- **Dec 2011:** Phase 2 started in Asia (India)
- **Oct 2012:** All CSR’s completed

- **Apr 2010:** Phase 1 started
- **Mar 2011:** Phase 2 started in Asia (Pakistan)
- **Oct 2011:** Phase 2 started in Asia (Philippines)
- **Feb 2012:** Immunizations completed
### Phase 1 & dose ranging studies in EU adults (1)

#### Study design

**Clinical Site:**
Center for Evaluation of Vaccines
University of Antwerp – Belgium
PI: Prof. Pierre Van Damme

**First in Man Trial**

<table>
<thead>
<tr>
<th>Group</th>
<th>Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Vi-CRM$_{197}$ conjugate (25.0 µg/dose)</td>
</tr>
<tr>
<td>B</td>
<td>Typherix (25.0 µg/dose)</td>
</tr>
</tbody>
</table>

**Dose Ranging trial**

<table>
<thead>
<tr>
<th>Group</th>
<th>Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Vi-CRM$_{197}$ conjugate (12.5 µg/dose)</td>
</tr>
<tr>
<td>B</td>
<td>Vi-CRM$_{197}$ conjugate (5.0 µg/dose)</td>
</tr>
<tr>
<td>C</td>
<td>Vi-CRM$_{197}$ conjugate (1.25 µg/dose)</td>
</tr>
<tr>
<td>D</td>
<td>Typherix (25.0 µg/dose)</td>
</tr>
</tbody>
</table>

Source: Van Damme et al. PLoS ONE 2011; 6 (9): e25398 doi; 10.1371
Phase 1 & dose ranging studies in EU adults (2)

Anti-Vi serum IgG 28 days after vaccination

Log2 scale


Selected for further clinical evaluation
### Phase 2 clinical studies in endemic countries (1)

**Study Design**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>1° dose</th>
<th>2° dose</th>
<th>3° dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults 18-45 y</td>
<td>Vi-CRM</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vi-PS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children 24-59 mo</td>
<td>Vi-CRM</td>
<td>Vi-CRM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vi-PS</td>
<td>Prevenar</td>
<td></td>
</tr>
<tr>
<td>Older Infants 9 mo</td>
<td>Vi-CRM + EPI</td>
<td>Vi-CRM</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prevenar + EPI</td>
<td>Prevenar</td>
<td></td>
</tr>
<tr>
<td>Infants 6 wks</td>
<td>Vi-CRM + EPI</td>
<td>Vi-CRM + EPI</td>
<td>Vi-CRM + EPI</td>
</tr>
<tr>
<td></td>
<td>Prevenar+EPI</td>
<td>Prevenar+EPI</td>
<td>Prevenar+EPI</td>
</tr>
</tbody>
</table>

* Doses 8 weeks apart in children & and older infants
** Doses 4 weeks apart in infants
### Phase 2 clinical studies in endemic countries (2)

**Clinical Sites and population enrolled**

<table>
<thead>
<tr>
<th>PAKISTAN</th>
<th>INDIA</th>
<th>PHILIPPINES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aga Khan University Karachi, Pakistan</td>
<td>KEM Hospital Pune, India</td>
<td>Research Institute for Tropical Medicine Manila, Philippines</td>
</tr>
<tr>
<td>PI: Prof Zulfiqar Buttha</td>
<td>PI: Prof Ashish Bavdekar</td>
<td>PI: Prof Rose Capeding</td>
</tr>
<tr>
<td>Prof Sajid Soofi</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults 18-45 years</td>
<td>Adults 18-45 years</td>
<td></td>
</tr>
<tr>
<td>Children 24-59 months</td>
<td>Children 24-59 months</td>
<td></td>
</tr>
<tr>
<td>Older Infants 9 months</td>
<td>Older Infants 9 months</td>
<td></td>
</tr>
<tr>
<td>Infants 6 weeks</td>
<td>Infants 6 weeks</td>
<td></td>
</tr>
</tbody>
</table>
## Overall safety profile in endemic countries trials

*Pakistan, India & Philippines, combined data*

<table>
<thead>
<tr>
<th>Vaccine</th>
<th># subjects</th>
<th># doses</th>
<th>Any death</th>
<th>Any SAE*</th>
<th>Any Local</th>
<th>Any systemic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vi-CRM\textsubscript{197}</td>
<td>40 adults</td>
<td>40</td>
<td>0</td>
<td>0</td>
<td>19 (48%)</td>
<td>20 (50%)</td>
</tr>
<tr>
<td></td>
<td>40 children</td>
<td>80</td>
<td>0</td>
<td>2 (5%)</td>
<td>23 (58%)</td>
<td>16 (40%)</td>
</tr>
<tr>
<td></td>
<td>40 older infants</td>
<td>80</td>
<td>0</td>
<td>4 (10%)</td>
<td>9 (23%)</td>
<td>18 (45%)</td>
</tr>
<tr>
<td></td>
<td>40 infants</td>
<td>120</td>
<td>0</td>
<td>5 (13%)</td>
<td>34 (85%)</td>
<td>33 (83%)</td>
</tr>
<tr>
<td>Control</td>
<td>40 adults</td>
<td>40</td>
<td>0</td>
<td>0</td>
<td>20 (50%)</td>
<td>20 (50%)</td>
</tr>
<tr>
<td></td>
<td>40 children</td>
<td>80</td>
<td>0</td>
<td>2 (5%)</td>
<td>22 (55%)</td>
<td>18 (45%)</td>
</tr>
<tr>
<td></td>
<td>40 older infants</td>
<td>80</td>
<td>0</td>
<td>5 (13%)</td>
<td>21 (53%)</td>
<td>29 (73%)</td>
</tr>
<tr>
<td></td>
<td>39 infants</td>
<td>117</td>
<td>0</td>
<td>4 (10%)</td>
<td>31 (79%)</td>
<td>28 (72%)</td>
</tr>
</tbody>
</table>

* No Serious Adverse Event was vaccine related
Immunogenicity in Adults is similar in Europe and Asia

Anti-Vi serum IgG 28 days after vaccination

Log2 scale

Europe

India & Pakistan combined data

ELISA GMC

Vi-PS 25μg Vi-CRM$_{197}$ 5μg
Vi-CRM197 (5µg) in 9 month infants vs. Vi-PS (25µg) in adults

Anti-Vi serum IgG 28 days after vaccination

Vi-PS: All adults from NVGH studies in endemic countries combined
Vi-CRM$_{197}$: Older infants from NVGH studies in endemic countries combined
NVGH proposed basis for WHO pre-qualification

- Field trials with the Vi-PS vaccines and Vi-rEPA have consistently shown that anti-Vi IgG serum antibodies confer protection against typhoid fever.

- The investigators of the Vi-rEPA efficacy trial defined serological correlates of protection (i.e., threshold of anti-Vi antibody levels which correlates with clinical protection)

- Therefore, the prequalification of ViCP-CV could be based on immunogenicity data (i.e., without a pre-licensure efficacy trial with clinical endpoints)

- Regulatory wise, two approaches should be considered:
  - ViCP-CV induce protective titers in children <2 years. Sero-protection rates can be calculated by correlating the manufacturer’s ELISA data with the NIH ELISA data used to define serological correlates of protection in the Vietnamese efficacy trial
  - Immunogenicity of ViCP-CV in <2 years is not inferior than that of the licensed Vi-PS in >2 years (i.e., age groups where the clinical efficacy of Vi-PS was shown and the vaccine is licensed)

- Following registration and pre-qualification, larger post marketing surveillance studies should be undertaken to further assess vaccine effectiveness and long term safety
Conclusions

- NVGH studies show that Vi-CRM$_{197}$ is a safe and well tolerated vaccine in all age groups.

- NVGH studies show that Vi-CRM$_{197}$ is immunogenic in infants and inclusion of a typhoid vaccine into WHO EPI schedules is a concrete possibility.

- NVGH is ready to pass the baton to an Asian manufacturer to complete development, obtain licensure, achieve WHO pre-qualification and start distribution.
Acknowledgements

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