Status of SII Bovine Rotavirus Pentavalent Vaccine (BRV-PV)

Dr Prasad Kulkarni, MD
Serum Institute of India Limited  Pune

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Outline

- Origins of BRV
- Development so far
- Results in nutshell
- Phase III studies
- Future plans
Origins of the BRV

- NIAID developed single gene reassortants of the bovine rotavirus UK Compton strain (G6P5[7]) as the backbone
- Four reassortant viruses with
  - A single gene for VP7 of either a G1, G2, G3, or G4 human serotype and
  - 10 genes from the bovine rotavirus UK strain
- Three clinical studies demonstrated its safety and immunogenicity
- Tech transfer to SIIL in 2005
- SIIL developed a hexavalent formulation (G1, G2, G3, G4, G8, G9) for toxicity studies
- Clinical development with a pentavalent formulation (G1, G2, G3, G4, G9)
Bovine human reassortants

Human Rotavirus (HRV) x Bovine RV Reassortant Hexavalent Vaccine with VP7 Serotype 1, 2, 3, 4, 8, and 9 Specificities

Diagram showing the reassortment process of HRV and Bovine RV to create a vaccine with specific VP7 serotypes.
Sterile, pentavalent, lyophilized powder
- rotavirus reassortants G1, G2, G3, G4 and G9 along with stabilizer
- 2.5 ml antacid as diluent containing sodium bicarbonate and sodium citrate for oral administration.
- stable for
  - three years at 2 to 8°C, and 25°C,
  - for two years at 37°C, and
  - for six months at 40°C.
## Development so far

<table>
<thead>
<tr>
<th>Phase</th>
<th>Objective</th>
<th>No. of doses</th>
<th>FFU/Serotype/Dose</th>
<th>Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Clinical</td>
<td>Safety</td>
<td>Single and repeated</td>
<td>$10^7$</td>
<td>Rabbits and Rats</td>
</tr>
<tr>
<td>Phase I</td>
<td>Safety</td>
<td>1</td>
<td>$10^6$</td>
<td>18 adults, 18 toddlers, 18 infants</td>
</tr>
<tr>
<td>Phase IIa</td>
<td>Safety</td>
<td>3</td>
<td>$10^{5.2}$</td>
<td>60 infants</td>
</tr>
<tr>
<td></td>
<td>Immunogenicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase IIb</td>
<td>Safety</td>
<td>3</td>
<td>$10^{5.6}$</td>
<td>60 infants</td>
</tr>
<tr>
<td></td>
<td>Immunogenicity</td>
<td></td>
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</tr>
</tbody>
</table>
Pre-clinical Studies

- Single and repeated dose studies by oral route
- Wistar Rats and New Zealand White Rabbits. (10^{6.5} FFU/Serotype/Dose)
- No potentially serious toxicity that would preclude the use in human Trials.
Phase I Clinical Trial

- Double-blind, randomized, placebo-controlled, single dose ($10^6$ FFU/Serotype/Dose) study
- Sequentially in healthy adults, toddlers and infants
- 18 subjects in each group with 2:1 random allocation
- BRV-PV was safe and well tolerated. No SAE.
- Few mild and transient adverse events.
- Related events - nausea, loss of appetite, diarrhoea and vomiting
- No significant effect on lab parameters, No shedding
- a small immune response (28%) in infants.
Phase IIa study

- Randomized, double-blind, placebo controlled (1:1 ratio)
- 3 doses of $10^{5.2}$ FFU/serotype in 60 healthy infants.
- the vaccine was safe and well tolerated.
- Almost all the events were mild and transient.
- Two SAEs (UTI and septicemia) unrelated to study vaccines recovered uneventfully.
- No effect on laboratory parameters.
Reactogenicity of $10^{5.2}$ FFU/serotype BRV-PV

<table>
<thead>
<tr>
<th>Solicited Symptom</th>
<th>BRV-PV</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants assessed</td>
<td>27</td>
<td>30</td>
</tr>
<tr>
<td>At least one solicited symptom,</td>
<td>14 (51.85%)</td>
<td>21 (70.00%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (3.70%)</td>
<td>2 (6.67%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11 (40.74%)</td>
<td>13 (43.33%)</td>
</tr>
<tr>
<td>Fever</td>
<td>3 (11.11%)</td>
<td>8 (26.67%)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>5 (18.52%)</td>
<td>5 (16.67%)</td>
</tr>
<tr>
<td>Decreased Activity</td>
<td>4 (14.81%)</td>
<td>1 (3.33%)</td>
</tr>
<tr>
<td>Irritability</td>
<td>9 (33.33%)</td>
<td>12 (40.00%)</td>
</tr>
<tr>
<td>Respiratory Symptoms</td>
<td>5 (18.52%)</td>
<td>9 (30.00%)</td>
</tr>
<tr>
<td>Antipyretic Use</td>
<td>4 (14.81%)</td>
<td>7 (23.33%)</td>
</tr>
</tbody>
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Seroconversion with $10^{5.2}$ FFU/serotype BRV-PV

<table>
<thead>
<tr>
<th>Study arm</th>
<th>Post Dose 2</th>
<th>Post Dose 3</th>
</tr>
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<tbody>
<tr>
<td>SII BRV-PV</td>
<td>9/25 (36.00%)</td>
<td>12/25 (48.00%)</td>
</tr>
<tr>
<td>Placebo</td>
<td>2/28 (7.14%)</td>
<td>6/28 (21.43%)</td>
</tr>
<tr>
<td>p Value*</td>
<td>0.0160</td>
<td>0.0492</td>
</tr>
</tbody>
</table>

*Fisher's Exact Test.

Post dose 3 GMTs in vaccine and placebo arms were 18.55 U/ml; and 7.31 U/ml.
Phase IIb study

- Randomized, double-blind, placebo controlled (1:1 ratio)
- assessed three doses of $10^{5.6}$ FFU/serotype in 60 healthy infants.
- the vaccine was safe and well tolerated.
- Almost all the events were mild and transient.
- No SAEs.
- No effect on laboratory parameters.
# Reactogenicity of $10^{5.6}$ FFU/serotype BRV-PV

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<td>Participants Assessed</td>
<td>30</td>
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<tr>
<td>At least one Solicited Symptoms</td>
<td>18 (60.00%)</td>
<td>20 (66.67%)</td>
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<td>Diarrhea</td>
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**Seroconversion with $10^{5.6}$ FFU/serotype BRV-PV**

**Study arm**

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<tr>
<td>SII BRV-PV</td>
<td>17/30 (56.67%)</td>
<td>18/30 (60.00%)</td>
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<tr>
<td>Placebo</td>
<td>3/26 (11.54%)</td>
<td>2/26 (7.69%)</td>
</tr>
<tr>
<td>p Value*</td>
<td>0.0006</td>
<td>0.0001</td>
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*p Value* indicates statistical significance.

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*Fisher's Exact Test.

Post dose 3 GMTs in vaccine and placebo arms were 13.58 U/ml; and 0.85 U/ml. Results in line with published studies.
Phase III efficacy study - India

- A double blind, placebo controlled, multi-centric Phase 3 study
- Sample size – 7500 infants; event driven trial
- 1:1 randomization to vaccine : placebo
- Multicentre in India
- Vaccination at 6, 10 and 14 weeks of age concurrently with UIP vaccines
- Follow up till 2 years of age
Phase III efficacy study - India

- to demonstrate that the vaccine is efficacious against severe rotavirus gastroenteritis in Indian infants
- Weekly home visits
- Approved by DCGI, HMSC and ethics committees
- Initiated on 9 May 2014
- > 1000 infants recruited so far
- Data on first 500 shows no safety concern
- DSMB oversight on safety issues
Phase III timelines

- Study initiation – 9 May 2014
- Complete enrolment – March 2015
- Study completion – March 2017
- Interim analysis – 122 cases of severe rotavirus GE
Phase III efficacy study - Niger

- A double blind, placebo controlled, Phase 3 study
- In Niger by Epicentre
- Sample size – 7770 infants; event driven trial
- 1:1 randomization to vaccine: placebo
- Vaccination at 6, 10 and 14 weeks of age concurrently with EPI vaccines
- Follow up till 2 years of age
Phase III efficacy study - Niger

- to demonstrate that the vaccine is efficacious against severe rotavirus gastroenteritis in African infants
- Weekly home visits
- Approved by Niger NRA, WIRB and WHO ERC
- Initiated on 9 July 2014
- > 600 infants recruited so far
- DSMB oversight on safety issues
Phase III EPI study

- A double blind, placebo controlled, multi-centric Phase 3 study
- Sample size – 1500 infants;
- 1:1 randomization to vaccine : placebo
- Multicentre in India
- Vaccination at 6, 10 and 14 weeks of age concurrently with UIP vaccines
Phase III EPI study

- to demonstrate
  - Non-interfere with immune response of UIP vaccines
  - Lot-to-lot consistency
- Submitted to DCGI, HMSC and ethics committees
- DSMB oversight on safety issues
- Hope to start early next year
Future plans

- Apart from the lyophilized presentation, SIIL is working on a fully liquid; ready-to-use vaccine
- contains the reassortants of the same serotypes.
- Animal toxicity studies started in June 2014.
- Phase I trial – Q2 2015
Acknowledgements

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  - Late Albert Kapikian; NIAID,
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  - Sanjay Lalwani; BVMC, Pune

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