Phase 3 efficacy study of a new pentavalent bovine-human reassortant rotavirus vaccine in India

12th International Rotavirus Symposium
7-9 September 2016, Melbourne

Dr Prasad Kulkarni, MD
Serum Institute of India Limited  Pune
Overview

• SIIPL Rotavirus vaccine programme
• Lyophilized clinical development
  • Phase III efficacy study
• Liquid clinical development
• Summary
R&D Program

- Bovine human reassortant rotavirus vaccine originally developed by NIAID
- Bovine rotavirus UK-Compton strain (G6P5[7]) as the backbone
- Reassortants with different VP7 encoding genes to generate different G-types (G1, G2, G3, G4 & G9)
- SIIL worked on the same technology and developed
  - Lyophilized Pentavalent Rotavirus vaccine
  - Liquid Pentavalent Rotavirus vaccine
## Composition

<table>
<thead>
<tr>
<th>Role of Components</th>
<th>List of Components</th>
<th>Liquid</th>
<th>Lyophilized</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immunizing agent (Live Human and Bovine Rotavirus Reassortants)</strong></td>
<td>G1 (D X UK)</td>
<td>( &gt;10^{5.6} ) FFU</td>
<td>( &gt;10^{5.6} ) FFU</td>
</tr>
<tr>
<td></td>
<td>G2 (DS-1 X UK)</td>
<td>( &gt;10^{5.6} ) FFU</td>
<td>( &gt;10^{5.6} ) FFU</td>
</tr>
<tr>
<td></td>
<td>G3 (P X UK)</td>
<td>( &gt;10^{5.6} ) FFU</td>
<td>( &gt;10^{5.6} ) FFU</td>
</tr>
<tr>
<td></td>
<td>G4 (ST-3 X UK)</td>
<td>( &gt;10^{5.6} ) FFU</td>
<td>( &gt;10^{5.6} ) FFU</td>
</tr>
<tr>
<td></td>
<td>G9 (AU32 X UK)</td>
<td>( &gt;10^{5.6} ) FFU</td>
<td>( &gt;10^{5.6} ) FFU</td>
</tr>
<tr>
<td></td>
<td>Eagle's MEM with Hank's Salts</td>
<td>11.66 mg</td>
<td>( \leq 6.63 ) mg</td>
</tr>
<tr>
<td><strong>Cell Culture Medium</strong></td>
<td>Glutamine</td>
<td>0.38mg</td>
<td>0.20mg</td>
</tr>
<tr>
<td></td>
<td>Sodium bicarbonate</td>
<td>1.65mg</td>
<td>64.9*</td>
</tr>
<tr>
<td></td>
<td>Sucrose</td>
<td>568 mg</td>
<td>50mg</td>
</tr>
<tr>
<td></td>
<td>Citric Acid</td>
<td>8 mg</td>
<td>24mg</td>
</tr>
<tr>
<td></td>
<td>Sodium citrate tribasic dihydrate</td>
<td>60 mg</td>
<td>nil</td>
</tr>
<tr>
<td><strong>Excipients/Stabilizers</strong></td>
<td>ZnCl2</td>
<td>1.09 mg</td>
<td>nil</td>
</tr>
<tr>
<td></td>
<td>CaCl2</td>
<td>1.18 mg</td>
<td>nil</td>
</tr>
<tr>
<td></td>
<td>Gelatin</td>
<td>40.2 mg</td>
<td>nil</td>
</tr>
<tr>
<td></td>
<td>Potassium phosphate dibasic</td>
<td>32 mg</td>
<td>nil</td>
</tr>
<tr>
<td></td>
<td>Glycine</td>
<td>nil</td>
<td>50mg</td>
</tr>
<tr>
<td><strong>Base</strong></td>
<td>Water for Injection</td>
<td>( \sim 2.0 ) ml</td>
<td>( \sim 2.5 ) ml</td>
</tr>
</tbody>
</table>

MEM: Minimum Essential Medium used for growing VERO cells.
FFU: Fluorescent Focus Unit used for testing virus potency/titer
*64mg sodium bicarbonates is present in diluents of rotavirus vaccine
Lyophilized Pentavalent Rotavirus vaccine
Proposed Package – Contents

Single dose Lyophilized vaccine in vial

Diluent (Citrate – Bicarbonate buffer) in vial

3 mL Oral syringe – (Needle cannot be fitted)

An adapter to transfer diluent into vaccine vial
Stability Summary

• Drug Product (lyophilized vaccine)
  - 36 months at 5 ±3°C,
  - 36 months at 25°C
  - 18 months at 37°C
  - 18 months at 40°C

• Reconstituted Vaccine
  - Should be used before 8 hours if stored at 2 to 8°C.
Liquid Pentavalent Rotavirus vaccine
Product Profile

- Live-Oral, pentavalent Liquid with VVM7
- Formulation with final container (Lamiplast Plastic Tube) is finalized
- Volume 2 ml
- Stability studies are in progress
- Three commercial levels batch manufacturing are in progress
- Storage Temperature 2 to 8°C.
Proposed Package – Contents
Clinical Development of Lyophilized vaccine
<table>
<thead>
<tr>
<th>Phase</th>
<th>Objective</th>
<th>Number 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>$10^{6.62-7.79}$</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 &amp; Immunogenicity</td>
<td>3</td>
<td>$10^{5.2}$</td>
<td>60 infants</td>
</tr>
<tr>
<td>Phase IIb</td>
<td>Safety &amp; Immunogenicity</td>
<td>3</td>
<td>$10^{5.6}$</td>
<td>60 infants</td>
</tr>
</tbody>
</table>
Bovine rotavirus pentavalent vaccine development in India

Jagdish K. Zade, Prasad S. Kulkarni*, Sajjad A. Desai, Rajendra N. Sabale, Sameer P. Naik, Rajeev M. Dhere

Serum Institute of India Ltd., Pune, India
A double blind, placebo controlled, multi-centric Phase III study

Sample size–7500 infants; event driven trial

1:1 randomization to vaccine : placebo

Efficacy against severe rotavirus gastroenteritis

Primary analysis at 122 cases of SRVGE

Immunogenicity in a subset of subjects

Vaccination at 6, 10 and 14 weeks of age concurrently with UIP vaccines

Follow up till 2 years of age
Phase III Clinical Trial - Efficacy

- Six sites
- Each site has 70-100 study staff
- Weekly home visits by Field Workers
- Initiated on 9 May 2014
- Recruitment completed 10 April 2015
- DSMB oversight on safety issues
- IAC for intussusception
- Study completion Q2 2017
Phase III Clinical Trial – status

- Met with primary analysis and data analysis is ongoing
- CSR to be ready soon
- Will be submitted for Indian licensure as well as WHO PQ
Phase III Clinical Trial – Lot-to-Lot consistency

- A open label, active comparator controlled, multi-centric Phase III study
- To demonstrate
  - Lot-to-lot consistency
  - Non-interference with immune response of UIP vaccines
- Sample size – 1500 infants
- 1:1:1:1 randomization to 3 lots of BRV-PV: Rotarix
- Vaccination at 6, 10 and 14 weeks of age concurrently with UIP vaccines
Phase III Clinical Trial – Lot-to-Lot consistency

- Ten sites
- DSMB oversight on safety issues
- IAC for intussusception
- Initiated on 2 December 2015
- Recruitment completed - August 2016
- Study completion - Q2 2017
Clinical development of Liquid Formulation
## Clinical Development of LBRV

<table>
<thead>
<tr>
<th>Phase</th>
<th>Objective</th>
<th>No. of doses</th>
<th>FFU / Serotype/Dose</th>
<th>Vaccine recipients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Clinical</td>
<td>Safety</td>
<td>Single and repeated</td>
<td>( \log_{10} 6.6-6.7 )</td>
<td>Rabbits and Rats</td>
</tr>
<tr>
<td>I</td>
<td>Safety</td>
<td>1</td>
<td>( \geq \log_{10} 5.6 )</td>
<td>Adults</td>
</tr>
<tr>
<td>II/III</td>
<td>Safety and Immunogenicity</td>
<td>3</td>
<td>( \geq \log_{10} 5.6 )</td>
<td>Infants (Planned)</td>
</tr>
</tbody>
</table>
Phase I Clinical Trial

- Single center, open-label
- Single dose ($10^{5.6}$FFU/Serotype/Dose)
- Healthy adults - 20
- Primary objective: safety and tolerability
Results

• No immediate post-vaccination reactogenicity

• No solicited reactions within 7 days of post-vaccination.

• No unsolicited and serious adverse events within 28 days after vaccination.
Phase II/III Clinical trial

A Phase II/III, Multicenter, Open-label, Randomized Study of Liquid Bovine Rotavirus Pentavalent Vaccine (LBRV-PV) to Evaluate Lot-to-Lot Consistency and to Compare Non-inferiority with Lyophilized BRV-PV in Healthy Infants in India
Design

- A open label, randomized, active comparator controlled, multi-centric Phase III study
- To demonstrate
  - Lot-to-lot consistency
  - Non-inferiority to Lyophilized BRV-PV
- Sample size – 1500 infants
- 1:1:1:1 randomization to 3 lots of BRV-PV : Lyophilized BRV-PV
- Vaccination at 6, 10 and 14 weeks of age concurrently with UIP vaccines
Phase II/III Clinical trial – Timelines

- DCGI Submission – Q4 2016
- DCGI approval expected – Q1 2017
- Study Initiation – Q2 2017
- Enrolment completion – Q4 2017
- Results to be ready – Q1 2018
BRV technology developed by NIAID

SII worked on this technology and made lyophilized and liquid pentavalent vaccines

Phase III results of lyophilized vaccine should be available soon

Liquid vaccine should enter Phase III trial by Q1 2017
Collaborative Effort

Enterovirus Research Centre, Mumbai

Investigators and study staff
Thank you