Heat Stable Rotavirus Vaccine
A thermostable rotavirus vaccine approach

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A Pioneer in Vaccine Development

Maurice R. Hilleman, PhD, DSc
Senior Vice President, 1957-1984
Merck Sharp & Dohme Research Laboratories

- Founded by MSD (Merck & Co) and Wellcome Trust in 2009, in New Delhi, India
- Global vaccine R&D organization focused on making high-impact affordable vaccines

Hilleman Labs has developed a Heat stable rotavirus vaccine to allow for greater stability and reduce cold chain burden
Overview

1. Introduction: Hilleman’s Heat Stable Rotavirus Vaccine
   i. Background
   ii. Target Product Profile
   iii. Dual-chamber Presentation

2. Clinical Development
   I. Clinical Development Plan
   II. Results from Phase 1 adult
   III. Next Steps
Background

• Inadequate immunization supply chain in LMICs*
  • 2011- 2.8million vaccine doses lost due to inadequate cold chain
  • Nigeria 2011- 41% of fridges were non-functional
  • Ethiopia 2013- 30% of cold chain equipment non functional
  • WHO 2013- less than 10% of countries have WHO requirement of effective vaccine management Practice

• 2013 Cold Chain system in India**:
  – 10 states, the largest district and the one most distant from the state capital;
  – Marked vaccine boxes were used to monitor temperature with data loggers
  – 4 storage facilities (National, State, District and Field) including transport

RESULTS
  – Showed temperature excursions above 8 °C in more than 50% of states
  – Occurred at every level of vaccine storage
  – Average deviation 15 °C for 17-146 days (maximum temp recorded 20.9 °C)

• Inadequate Supply of affordable vaccine

* IMMUNIZATION SUPPLY CHAIN AND LOGISTICS; A neglected but essential system for national immunization program; WHO/IVB/14.05; 2014
**Bull World Health Organ 2013;91:906–913
## Proposed Product Profile – Heat Stable Rotavirus Vaccine

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Description</td>
<td>Live oral pentavalent lyophilized (RotaTeq antigen bulk) vaccine provided with diluent for the prevention of rotavirus gastroenteritis.</td>
</tr>
<tr>
<td>Indication</td>
<td>Same as RotaTeq</td>
</tr>
<tr>
<td>Target Population</td>
<td>Indicated for infants between the ages of 6 to 32 weeks.</td>
</tr>
<tr>
<td>Administration</td>
<td>3 doses administered orally starting at 6 to 12 weeks of age, with the subsequent doses administered at 4- to 10-week intervals.</td>
</tr>
<tr>
<td>Safety/ Tolerability</td>
<td>Similar to RotaTeq.</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Immunobridging, non inferior to RotaTeq.</td>
</tr>
<tr>
<td>How supplied/ Formulation</td>
<td>Supplied in two chambered Integrated Reconstitution and Administration Device (IRAD) as a single dose</td>
</tr>
<tr>
<td>Storage</td>
<td>Room temperature away from direct sunlight.</td>
</tr>
</tbody>
</table>
## Heat stability of HSRV

<table>
<thead>
<tr>
<th>Condition</th>
<th>Real time Stability</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-8°C</td>
<td>&gt; 3 years</td>
</tr>
<tr>
<td>25°C</td>
<td>&gt; 3 years</td>
</tr>
<tr>
<td>37°C</td>
<td>20 months</td>
</tr>
<tr>
<td>45°C</td>
<td>&gt; 6 months</td>
</tr>
</tbody>
</table>
Integrated Reconstitution and Administration Device

Milled Lyophilized Powder and Diluent in a two component pack

Powdered vaccine

Antacid / Diluent

Tear-off cap on Spout

‘Packaged in a single component/ready to use format’ thereby meeting PSPQ – Critical characteristic
User feedback Studies
Integrated Reconstitution and Administration Device: User Acceptability Trial (study)

First Generation Prototype
• City of Pune, India
• 8 Pediatricians, 18 General Physicians, 51 nurses, 10 Pharmacists, 13 cold storage managers
• Three types of Health care setup
  • Rural, Semi Urban and Urban

Key observations:
• 84% responders believed
  • Suitable for paediatric vaccine administration;
  • by one hand and
  • have appropriate ergonomic

Design improvements suggested

Second Generation Improved design
Study 2 ongoing
• Conducted at multiple sites in India
• Healthcare staff involved in Vaccination
  • Doctors
  • Vaccinators
  • Nurses
  • Social/ Health workers

Observations:
• Operating the device
• Intuitiveness for use
• Post administration observations; waste disposal, safety of the infant during vaccination/ vaccine administrator

Completed at 3 site with high level of acceptance
HSRV: Clinical Development Strategy
Clinical Development: HSRV Program

• Preclinical
  – Regulatory Toxicology (completed)

  Established bulk product with no dose/dosage titration/ schedule evaluation

• Phase I/II
  – Evaluate simultaneously the safety and immunogenicity of vaccine.
  – In adults for single dose (safety only), 3 doses in infants

• Phase IIb immuno-bridging in infants
  – Non inferiority design with RotaTeq
  – Interaction with EPI vaccines
  – Lots consistency
  – Safety subset
  – Temperature aged arm, out of cold chain

• Phase IV (PMS)

Licensure and PSF submission for WHO PQ
Phase I/II pilot study: Overview

• **Study title:** A randomized phase I/II study to evaluate safety and reactogenicity of a single dose of lyophilized live attenuated pentavalent (G1-G4 and P[8]) heat-stable rotavirus vaccine (HSRV), in healthy adult volunteers; followed by evaluation of the safety, reactogenicity and immunogenicity of a 3-dose series in infants age 6-8 weeks

• **Principal Investigator:** Dr. K Zaman

• **Clinical Study Center:** Center for Communicable Diseases, icddrb, Dhaka, Bangladesh

• **Study design:**
  – Adult Cohort: 50 subjects; Double-blind, randomized, single dose, placebo-controlled study
  – Infant Cohort: 50 subjects; Open labelled, randomized, active (RotaTeq) control (3 dose series staggered with EPI vaccines)
Primary Objective:
• To assess the reactogenicity of a single oral dose of lyophilized HSRV vaccine vs placebo,
  • Solicited adverse events (AEs) up to 8 days post vaccination.
  • Unsolicited AEs and serious adverse events (SAEs) throughout the duration of study.

Secondary Objective:
• To assess the frequency and duration of post-vaccination shedding rotavirus in stool samples in adults on day 3, 5 and 7 after single dose of investigational vaccine.
Study Procedure (adult cohort)

- Vaccine research Unit at icddrb

- All enrolled participants received a single oral dose of HSRV vaccine or placebo dose and observed closely for at least 30 minutes following dose administration.

- All solicited AEs (nausea, diarrhoea, abdominal pain, vomiting, fever and cough & running nose) during the 8-day (Day 0 – Day 7) follow-up period were recorded.

- All unsolicited AEs and SAEs occurring during the 15-day (Day 0 – Day 14) follow-up period were recorded.

- No blood samples were collected in this study.

- Stool samples were collected on day 3, 5 and 7 after single dose of investigational vaccine/placebo administration for determining shedding of rotavirus by ELISA.
Results: Adult Cohort
Total vaccinated cohort: Adult

<table>
<thead>
<tr>
<th>Number of participants vaccinated, completed and withdrawn</th>
<th>Placebo</th>
<th>HSRV</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Participants vaccinated</td>
<td>24</td>
<td>26</td>
<td>50</td>
</tr>
<tr>
<td>Number of Participants completed</td>
<td>24</td>
<td>26</td>
<td>50</td>
</tr>
<tr>
<td>Number of Participants withdrawn</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Summary of demographic characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Parameters or Categories</th>
<th>Placebo (N = 24)</th>
<th>HSRV (N = 26)</th>
<th>Total N = 50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Minimum</td>
<td>21</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Maximum</td>
<td>37</td>
<td>41</td>
<td>41</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>13</td>
<td>15</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>11</td>
<td>11</td>
<td>22</td>
</tr>
</tbody>
</table>
Safety analysis: Adult Cohort
Adverse Event Summary : Adult Cohort

Participants reporting any AE (solicited) during the 8-day (Day 0-7) Post-Vaccination Period (Total Vaccinated Cohort)

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>N</th>
<th>%</th>
<th>LL</th>
<th>UL</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSRV</td>
<td>26</td>
<td>6</td>
<td>23.1</td>
<td>9.0</td>
<td>43.7</td>
</tr>
<tr>
<td>Placebo</td>
<td>24</td>
<td>2</td>
<td>8.3</td>
<td>NC</td>
<td>NC</td>
</tr>
</tbody>
</table>

N= number of Participants with the administered dose
n (%)= number (percentage) of Participants presenting at least one type of symptom
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit, NC = Not calculable
Solicited Adverse Events : Adult Cohort

Percentage of participants reporting each solicited general symptom through the 8-day (Days 0-7)

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Placebo (N=24)</th>
<th>HSRV (N= 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>1 (4.2)</td>
<td>4.2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (4.2)</td>
<td>4.2</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>1 (4.2)</td>
<td>4.2</td>
</tr>
<tr>
<td>Fever</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cough and running nose</td>
<td>1 (4.2)</td>
<td>4.2</td>
</tr>
</tbody>
</table>

n (%)= number (percentage) of participants reporting at least once the symptom
### Solicited Adverse Events: Adult Cohort

Solicited adverse events with respect to seriousness, intensity, and causality.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Placebo (N = 24)</th>
<th>HSRV (N = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seriousness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Serious</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>Intensity*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Moderate</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Mild</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>Relationship</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inconsistent/Unrelated</td>
<td>4</td>
<td>14</td>
</tr>
</tbody>
</table>
# Unsolicited adverse events: Adult Cohort

Percentage of participants reporting the occurrence of unsolicited symptoms within the 15-day (Day 0 – Day 14)

<table>
<thead>
<tr>
<th>Primary System Organ Class (CODE)</th>
<th>Preferred Term (CODE)</th>
<th>Placebo N = 24</th>
<th>HSRV N = 26</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one symptom</td>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Diarrhoea</td>
<td>1</td>
<td>4.2</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Vomiting</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)

n (%) = number (percentage) of participants reporting at least once the symptom
Unsolicited Adverse Event: Adult Cohort

Unsolicited Adverse events with respect to seriousness, intensity, and causality

<table>
<thead>
<tr>
<th></th>
<th>CLASSIFICATION</th>
<th>Placebo (N = 24)</th>
<th>HSRV (N = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SERIOUSNESS</td>
<td>NOT SERIOUS</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>INTENSITY*</td>
<td>SERIOUS</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>MILD</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>MODERATE</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>SEVERE</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>RELATIONSHIP</td>
<td>INCONSISTENT UNRELATED</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

None of the participants experienced any SAEs and there were no fatal cases reported in the study
Conclusion and Summary: Adult Cohort

- Overall there were 6 (23.1%) participants in HSRV group who reported at least one solicited AE and 2 (8.3%) in placebo group.
- There were no reports of any Grade 3 symptoms.
- All solicited AEs (both solicited and unsolicited) were mild to moderate in intensity and resolved without any sequela
- None of the symptoms reported were assessed to be causally related to vaccination.
- None of the participants experienced any SAEs in the study
- There were no safety concerns raised based on the safety data
- After DSMB clearance rest of the trial subjects (infants) enrollment initiated
Next Steps

Completion of ongoing Phase I/II study infant cohort

- Expected completion of study: Dec 2016

• Phase IIb immuno-bridging study
  (Infants of 6-8 weeks, 3 doses)
  - Non Inferiority with RotaTeq
    • Co administration with other EPI vaccines
  - Larger safety cohort
    • 3000 subjects
    • 6 months follow up for AEs
  - Lot-to-lot consistency
    • 3 formulation lots with equivalence margin of 10% both sides
  - Out of cold chain use of vaccine

• WHO Pre Qualification
Thank you!
Conducted market research in 4 GAVI countries
- Bangladesh
- Burkina-Faso
- Côte d’Ivoire
- India

Methodology
Close-ended questions with 39 decision makers, and vaccinator/end users international opinion leaders
1. Feedback on field benefit of Heat stable formulation and innovative presentation
2. Rotavirus vaccines schedules, funding allocation, NITAG recommendation and stocking/ storage capabilities

Key Findings:
• HSRV as very positive development for use in field settings.
• Dual Chamber pouch device was seen as impactful. Lack of precedence of a was not seen as a concern
• Respondents indicated that they would support HSRV purchase for the NIP.