Safety and immunogenicity of a parenteral P2-VP8 subunit rotavirus vaccine

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MRC: Respiratory and Meningeal Pathogens Research Unit

12th African Rotavirus Symposium, Johannesburg, July 30-August 1 2019
Rationale for non-replicating rotavirus vaccine (NRRV)

**Oral rotavirus vaccines**

- interference by high levels of transplacentally-acquired maternal rotavirus antibodies
- rotavirus antibodies in breast-milk
- co-administration of oral polio vaccine
- micronutrient deficiency
- enteric co-infections and microbiome
- concurrent diseases e.g. HIV infection
- host genetics

**NRRVs**

- bypass the need for intestinal replication
- may provide enhanced efficacy
- safety benefit - no increased risk of intussusception
- produced at low cost
- combination with other childhood vaccines
- safe in children with severe immunodeficiency
P2-VP8 rotavirus vaccine

» Developed at US NIH.
» Truncated VP8 subunit protein from human Wa strain (G1P[8]) fused to the tetanus toxin P2 epitope:
  > Expressed in E. coli
» Liquid formulation, adsorbed onto aluminum hydroxide adjuvant, administered intramuscularly.

Schematic diagram of rotavirus VP4 protein
Vaccine development

Pre-clinical development

Clinical development

First in human
Adults 18–45 yrs
Baltimore
Dec 2012–Oct 2013

VAC 013
Phase I/II
Toddlers and infants
Soweto, South Africa
Mar 2014–Oct 2015

- Safe and well tolerated
- Reduced viral shedding following Rotarix

VAC 041
Phase I/II
Adults, toddlers and infants
3 sites, Soweto, South Africa
Feb 2016–Dec 2017

P2-VP8-P[4],P[6],P[8]

Fix, Vaccine, 2015; Groome, Lancet ID, 2017
VAC 041 – trivalent P2-VP8 vaccine

» Trivalent vaccine, including P[4], P[6], and P[8] antigens (DS-1, 1076 and Wa).

» Dose 5µg to 30µg per serotype (15 to 90µg total antigen) - lack of a clear dose-response in previous study.

» Double-blind, randomized, placebo-controlled, descending-age, dose-escalation study to evaluate safety, tolerability and immunogenicity in adults, toddlers, and infants.


Respiratory and Meningeal Pathogens Research Unit (National PI/Site PI - Dr Michelle Groome)

Family Clinical Research Unit (FAM-CRU) (Site PI - Dr Julie Morrison)

Shandukani Research Centre (Site PI - Dr Lee Fairlie)
<table>
<thead>
<tr>
<th>Group</th>
<th>TV P2-VP8 Dose</th>
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<tr>
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<td></td>
</tr>
<tr>
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</tr>
<tr>
<td></td>
<td>Placebo</td>
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</tr>
<tr>
<td>A2</td>
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<td>12</td>
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<tr>
<td></td>
<td>Placebo</td>
<td>3</td>
</tr>
<tr>
<td>A Total</td>
<td></td>
<td>30</td>
</tr>
<tr>
<td>B Toddler</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B1</td>
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<td>12</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>3</td>
</tr>
<tr>
<td>B2</td>
<td>90 µg</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>3</td>
</tr>
<tr>
<td>B Total</td>
<td></td>
<td>30</td>
</tr>
<tr>
<td>C Infant</td>
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<td></td>
</tr>
<tr>
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<td>Placebo</td>
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<td>C Total</td>
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<td>48</td>
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<tr>
<td>D Infant</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>15 µg</td>
<td>138</td>
</tr>
<tr>
<td></td>
<td>30 µg</td>
<td>138</td>
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<tr>
<td></td>
<td>90 µg</td>
<td>138</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>138</td>
</tr>
<tr>
<td>D Total</td>
<td></td>
<td>552</td>
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</table>
- Cohorts A, B, C – Day 7 safety bloods collected
- Safety visits on day 7 post vaccination for Cohort A and days 3 and 7 for Cohorts B, C, D

Faecal shedding of Rotarix assessed during the week after the first dose – stool samples collected on day 5, 7 and 9 – subset at RMPRU only.
Objectives

» Primary Objectives:
  > Safety
  To evaluate the safety and tolerability of the trivalent P2-VP8 subunit rotavirus vaccine at escalating dose levels in healthy South African adults, toddlers and infants
  > Immunogenicity
  To evaluate the immunogenicity of the trivalent P2-VP8 subunit rotavirus vaccine at different dose levels in healthy South African infants

» Exploratory Objective:
  > Efficacy
  To evaluate the impact of the trivalent P2-VP8 subunit rotavirus vaccination on shedding of Rotarix subsequently administered in healthy South African infants (subset)
Primary safety endpoints

> Number of adverse events and serious adverse events through 28 days after the last study injection

> Number of vaccine-induced reactions within 7 days after each injection

  • Local - injection site pain/tenderness, redness, swelling, itching, local lymphadenopathy
  • Systemic - fever, vomiting, nausea, fatigue, chills and myalgia for adults; fever, vomiting, irritability, decreased activity, and decreased appetite for toddlers and infants

Note:

> Progression from adults, toddlers to infants and for dose escalation: Safety Review Committee evaluated clinical and laboratory safety data through 7 days after the 1st injection.

> DSMB oversight.
Primary immunogenicity endpoints

» IgG to P2-VP8 vaccine antigens
  > Three assays, one for each antigen – P[4], P[6] and P[8]
  > 4-fold rise in titer from baseline to 28 days after the 3rd vaccination
  > Results both unadjusted and adjusted for maternal antibody

» IgA to P2-VP8 vaccine antigens
  > Three assays, one for each antigen – P[4], P[6] and P[8]
  > 4-fold rise in titer from baseline to 28 days after the 3rd vaccination

» Neutralizing antibodies to the strains from which vaccine antigens derived
  > Assay strains – DS-1 (P[4]), 1076 (P[6]) and Wa (P[8])
  > 2.7-fold rise in titer from baseline to 28 days after the 3rd vaccination
  > Results both unadjusted and adjusted for maternal antibody
Cohort A: 30 adults (15 per cohort; safety analysis)
Cohort B: 30 toddlers (15 per cohort; safety analysis)
Cohort C and D:

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>15 µg</th>
<th>30 µg</th>
<th>90 µg</th>
<th>Total</th>
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<td>Randomized</td>
<td>139</td>
<td>140</td>
<td>140</td>
<td>139</td>
<td>558</td>
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<tr>
<td>Vaccinated</td>
<td>139</td>
<td>139</td>
<td>140</td>
<td>139</td>
<td>557</td>
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<tr>
<td>Completed Day 84 visit</td>
<td>133 (96%)</td>
<td>134 (96%)</td>
<td>134 (96%)</td>
<td>135 (97%)</td>
<td>536 (96%)</td>
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<tr>
<td>Day 84 blood collected/analyzed</td>
<td>130 (94%)</td>
<td>133 (95%)</td>
<td>133 (95%)</td>
<td>134 (96%)</td>
<td>530 (95%)</td>
</tr>
<tr>
<td>PP immune population</td>
<td>130 (94%)</td>
<td>132 (94%)</td>
<td>132 (94%)</td>
<td>134 (96%)</td>
<td>528 (95%)</td>
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</tbody>
</table>
Safety

No statistically significant differences observed between the treatment groups in the proportions of participants with local reactions, systemic reactions or unsolicited adverse events: all cohorts

<table>
<thead>
<tr>
<th>Infants</th>
<th>Placebo n (%)</th>
<th>15µg n (%)</th>
<th>30µg n (%)</th>
<th>90µg n (%)</th>
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</thead>
<tbody>
<tr>
<td>Any local reaction (Grade 2 or higher)</td>
<td>9 (6.5)</td>
<td>19 (13.7)</td>
<td>13 (9.3)</td>
<td>16 (11.5)</td>
</tr>
<tr>
<td>Any systemic reaction (Grade 2 or higher)</td>
<td>30 (21.6)</td>
<td>44 (31.7)</td>
<td>30 (21.4)</td>
<td>42 (30.2)</td>
</tr>
<tr>
<td>Any unsolicited AE (Grade 2 or higher)</td>
<td>19 (13.7)</td>
<td>24 (17.3)</td>
<td>18 (12.9)</td>
<td>20 (14.4)</td>
</tr>
<tr>
<td>Any SAE</td>
<td>8 (5.8)</td>
<td>13 (9.4)</td>
<td>6 (4.3)</td>
<td>8 (5.8)</td>
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<tr>
<td>Any AE related to product</td>
<td>3 (2.2)</td>
<td>2 (1.4)</td>
<td>3 (2.1)</td>
<td>2 (1.4)</td>
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</table>
Immunogenicity
(Per Protocol Population)
Anti-P2-VP8 IgG in infants

- **P[4]**
- **P[6]**
- **P[8]**

Unadjusted for decrease in maternal antibodies

Seroresponses for all 3 antigens (adjusted for maternal antibodies)
Anti-P2-VP8 IgA titers in infants

Seroresponses for all 3 antigens
Serum anti-P2-VP8 IgA and IgG seroresponses for all 3 antigens in adults and toddlers

**Adults**

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<thead>
<tr>
<th></th>
<th>IgA</th>
<th></th>
<th></th>
<th>IgG</th>
<th></th>
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<tr>
<td>Placebo</td>
<td><img src="chart1.png" alt="Chart" /></td>
<td>30µg</td>
<td><img src="chart2.png" alt="Chart" /></td>
<td>90µg</td>
<td><img src="chart3.png" alt="Chart" /></td>
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<tr>
<td>Day 28</td>
<td><img src="chart4.png" alt="Chart" /></td>
<td>Day 56</td>
<td><img src="chart5.png" alt="Chart" /></td>
<td>Day 84</td>
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**Toddlers**

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<tr>
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<td>Day 28</td>
<td><img src="chart10.png" alt="Chart" /></td>
<td>Day 56</td>
<td><img src="chart11.png" alt="Chart" /></td>
<td>Day 84</td>
<td><img src="chart12.png" alt="Chart" /></td>
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Serum Neutralizing Antibodies to Wa in infants

Neutralizing Antibodies to Wa in Infants - GMT and 95% CI Per-Protocol Population, unadjusted for decrease in maternal antibodies

Neutralizing antibody seroresponse against Rotavirus Strain Wa in Infants - Per-Protocol Population Adjusted for decay in maternal antibodies
Serum Neutralizing Antibodies to DS-1 in infants

Neutralizing Antibodies to DS-1 in Infants - GMT) and 95% CI Per-Protocol Population, unadjusted for decrease in maternal antibodies

Neutralizing antibody seroresponse against Rotavirus Strain DS-1 in Infants - Per-Protocol Population
Adjusted for decay in maternal antibodies
Serum Neutralizing Antibodies to 1076 in infants

Neutralizing Antibodies to 1076 in Infants - GMT) and 95% CI Per-Protocol Population, unadjusted for decrease in maternal antibodies

Neutralizing antibody seroresponse against Rotavirus Strain 1076 in Infants - Per-Protocol Population Adjusted for decay in maternal antibodies
Rotavirus shedding post-Rotarix - infants

» Proportion of infants shedding rotavirus (ELISA) 5, 7 or 9 days after administration of the first dose of Rotarix® (4 weeks after the 3rd P2-VP8/placebo injection).

» Subset – infants at RMPRU:

<table>
<thead>
<tr>
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<th>Placebo</th>
<th>15 µg</th>
<th>30 µg</th>
<th>90 µg</th>
<th>Total</th>
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<tr>
<td></td>
<td>53</td>
<td>52</td>
<td>56</td>
<td>56</td>
<td>217</td>
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</table>

Reduction compared to placebo (any of the three days):
- 15µg: 10% (95% CI: -36-40)
- 30µg: 27% (-14-53)
- 90µg: 42% (4-65)
Conclusions

» All dose-levels well tolerated and no safety signals.
» Excellent anti-P2-VP8 IgG across the three vaccine P-types.
» Very good neutralising antibody responses to Wa, DS-1 and 1076 strains.
» Broader anti-P2-VP8 IgG and neutralising antibody responses than demonstrated for the monovalent vaccine.
» Responses better after 3 doses compared to 2 doses.
» Anti-P2-VP8 IgA in infants lower than anticipated.
» Significantly fewer infants vaccinated with the 90µg dose shed rotavirus compared to placebo recipients.
Considerations for Future Development Plans

» Assessment of efficacy of the stand-alone vaccine.
» Exploration of prime-boost regimens of live, oral RV vaccines and the P2-VP8 vaccine.
» Development of co-formulated vaccine, combining other EPI/UIP vaccines and P2VP8 in a single injection, including clinical assessment.
» Licensure and WHO prequalification of stand-alone and/or co-formulated vaccine for global availability.
Assessment of Efficacy of the Standalone Vaccine

» CVIA 061
A double-blind, randomized, active comparator-controlled, group-sequential, multinational trial to assess the safety and efficacy of a trivalent P2-VP8 subunit rotavirus vaccine in prevention of severe rotavirus gastroenteritis in healthy infants
CVIA 061 Study Outline

- Multinational
  - Sites in Zambia, Malawi, Ghana and India

Stage 1 Enrollment
3,500 infants
4-6 months

Interim analysis
once accrue
>30 cases
SRVGE

Futility Criteria
Not Met

Stage 2 Enrollment
4,700 infants
6-8 months

Futility Criteria
Met

Close enrollment
Crossover vaccination of TV
P2-VP8 infants
Study closure

Primary analysis
once accrue >99 cases SRVGE or all reach 2 years of age

Final analysis after all participants reach 2 years of age
Acknowledgements

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Carol Taoushanis
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Data team
Laboratory team

Shandukani site

FAM-CRU site

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Allison Stanfill
Jorge Flores

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Len Dally

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Nicole Meyer
Brandi Phillips

NIH – vaccine development