Clinical Development of a Trivalent 
Salmonella Conjugate Vaccine (TSCV)

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Trivalent *Salmonella* Conjugate Vaccine (TSCV) Components

- *S.* Typhimurium COPS-FliC conjugate
- *S.* Enteritidis COPS-FliC conjugate
- *S.* Typhi Vi-TT conjugate (Typbar-TCV)
Phase 1 First-in-Human trial (Salmonella CVD 1000)

- Phase 1, adaptive, 3 dose-escalating cohorts & confirmatory cohort

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Vaccine</th>
<th>Dose of each COPS and of Vi (µg)</th>
<th>No. Subjects</th>
<th>Dose #1</th>
<th>Dose #2</th>
<th>Vaccination Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (Step 1)</td>
<td>Trivalent</td>
<td>6.25</td>
<td>8</td>
<td>Vaccine</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>0</td>
<td>2</td>
<td>Placebo</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>B (Step 2)</td>
<td>Trivalent</td>
<td>12.5</td>
<td>10</td>
<td>Vaccine</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>0</td>
<td>2</td>
<td>Placebo</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>C (Step 3)</td>
<td>Trivalent</td>
<td>25</td>
<td>12</td>
<td>Vaccine</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>0</td>
<td>2</td>
<td>Placebo</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>D (Expanded, confirmatory cohort)</td>
<td>Trivalent (highest, well-tolerated dose among cohorts A-C)</td>
<td>25</td>
<td>Vaccine</td>
<td>Vaccine</td>
<td>1 &amp; 29*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trivalent</td>
<td>25</td>
<td>10</td>
<td>Vaccine</td>
<td>Placebo</td>
<td>1 &amp; (29)*</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td></td>
<td></td>
<td>Placebo</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>N = 96</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

N = 22 enrolled

Interrupted by COVID-19 Pandemic

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Phase 1 FIH: No Safety Concerns
Phase 1 FIH: serum ELISA IgG

100% seroconversions† for all 3 primary aim antigens:
• SE COPS
• ST COPS
• Vi PS

† 4-fold or greater increase in titer, compared to baseline

Due to the pandemic, the duration of antibody response was documented as elevated ≥4-fold-rise from baseline at Day 450/510!
Phase 1 FIH: serum ELISA IgA

100% seroconversions† for all 3 primary aim antigens:
• SE COPS
• ST COPS
• Vi PS

† 4-fold or greater increase in titer, compared to baseline
Phase 1/2a Bridging (Salmonella CVD 2000)

- Phase 1 Randomized, Blinded, Placebo-controlled trial
- “new” cGMP lots of TSCV

<table>
<thead>
<tr>
<th>Group</th>
<th>No. Subjects</th>
<th>Study Product</th>
<th>S. Enteritidis (µg)</th>
<th>S. Typhimurium (µg)</th>
<th>S. Typhi Vi (µg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>25</td>
<td>Full-strength formulation TSCV</td>
<td>25</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>B</td>
<td>25</td>
<td>Half-strength formulation TSCV</td>
<td>12.5</td>
<td>12.5</td>
<td>25</td>
</tr>
<tr>
<td>C</td>
<td>15</td>
<td>Dilutional half-strength TSCV*</td>
<td>12.5</td>
<td>12.5</td>
<td>12.5</td>
</tr>
<tr>
<td>D</td>
<td>15</td>
<td>Placebo</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*formulation which bridges to First-in-Human Phase 1
Phase 1/2a Bridging: Safety

(remains blinded)

• Fully enrolled (n=80 evaluable) and all study visits completed
• No SAEs
• No halting rules
• No safety concerns
Phase 1/2a Bridging: Immunogenicity

Proportion of subjects per group who manifested ≥ 4-fold rises in antibody titer *S. Enteritidis* COPS, *S. Typhimurium COPS*, and *S. Typhi Vi* antigens

<table>
<thead>
<tr>
<th></th>
<th>7-days post-vaccination</th>
<th>28-days post-vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheese GMT</td>
<td>351</td>
<td>25,293</td>
</tr>
<tr>
<td>Chocolate GMT</td>
<td>334</td>
<td>17,847</td>
</tr>
<tr>
<td>Cookies GMT</td>
<td>1.55</td>
<td>130</td>
</tr>
<tr>
<td>Popcorn GMT</td>
<td>41,516</td>
<td>25,657</td>
</tr>
</tbody>
</table>

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Phase 2 Age de-escalation (Salmonella CVD 3000)

**PI:** Mili Tapia

**Sites:**
- Centre pour le Développement des Vaccins du Mali (CVD-Mali), Bamako, Mali
- Centro de Investigacao em Saude (CISM), Manhiça, Mozambique
- Kenya Medical Research Institute Center for Global Health (KEMRI-CGH), Kisumu, Kenya

**Participation Duration:**
- For Steps 1-3, ~6 months
- For Step 4, ~12 months to 18 months
Phase 2 Age-de-escalation (Salmonella CVD 3000)

Step 1A
20 - 35 yrs
N = 40

Step 1B
5 - 9 yrs
N = 40

Step 1C
24 - 59 mon
N = 40

Step 1D
16 - 23 mon
N = 80

Step 2A
12 – 16 mon
N = 120

Step 2B
8 – 11 mon
N = 120

Step 2A
12 – 16 mon
N = 120

Step 3
12 – 14 wks
N = 180
16 – 18 wks
N = 180

Step 4
Prime 12 – 18 wks
Boost at:
9 mon OR
12 mon OR
15-17 mon
N = 456
Two doses

Enrollment Status
N=185

(06DEC2023)
Phase 2: Blinded Safety Results

**Step 1A (20-25 yrs) and Step 1B (5-9 yrs)**

**Step 1C (24-59 mons) and Step 1D (16-23 mons)**

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Acknowledgments

- Mike Levine, Raphael Simon, Sharon Tennant, Andrew Lees
- Bharat Biotech (Yogeswara Rao, Gangadhara Naidu, Ravindra Kumar, Raches Ella, Sai Prasad, Krishna Mohan)
  - Pharmaron (Drs. Al-Ibrahim and Beckett)
  - Mili Tapia
  - CVD-Mali
  - CISM
  - KEMRI-CGH
  - Likak Research
  - Marcela Pasetti Lab
  - Marcelo Sztein Lab
  - Aly Kwon, Fleesie Hubbard
  - Khristine Bozylinski-Bulos, Lynnee Roane
- Supported by NIAID and Wellcome Trust
### Timeline of TSCV

- **2012**
  - Wellcome Trust: Strategic Translation Award
  - PI: Mike Levine

- **2013**

- **2014**

- **2015**

- **2016**
  - Began GLP Toxicology studies

- **2017**
  - 09JUN2017 FDA Pre-IND meeting

- **2018**

- **2019**
  - 28JUN2019 FDA IND submission

- **2020**
  - SARS-CoV-2

- **2021**
  - 09DEC2019 Phase 1 FIH, First Enrollment

- **2022**
  - 26SEP2022 Phase 1 Bridging, First Enrollment
  - 05APR2023 Phase 2 Age-Descending, First Enrollment

- **2023**

- **2024**

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Phase 1 FIH: C-Reactive Protein

Cohort 1: CRP

Cohort 2 CRP
Phase 1 FIH: serum ELISA IgG

100% seroconversions† for all 5 antigens:
• SE COPS
• ST COPS
• Vi PS
• SE FliC
• ST FliC

† 4-fold or greater increase in titer, compared to baseline
Phase 1 FIH: serum ELISA IgA

100% seroconversions† for 3 antigens:
• SE COPS
• ST COPS
• Vi PS

† 4-fold or greater increase in titer, compared to baseline

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Phase 1/2a Bridging: Safety

(remains blinded)

- No SAEs
- No halting rules
- No safety concerns

Figure 2i. C-Reactive Protein, CRP
Phase 2: Demographics for Steps 1A to 2B

- Cohort 1A - 05APR2023
- Cohort 1B - 29APR2023
- Cohort 1C – 23MAY2023
- Cohort 1D - 13JUNE2023

- Cohort 2A – 18JUL2023
- Cohort 2B – 07AUG2023

<table>
<thead>
<tr>
<th>Total Enrolled</th>
<th>Cohort 1A 20-35 y</th>
<th>Cohort 1B 5-9 y</th>
<th>Cohort 1C 24-59m</th>
<th>Cohort 1D 16-23m</th>
<th>Cohort 2A 12-16m</th>
<th>Cohort 2B 8-11m</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>80</td>
<td>120</td>
<td>120</td>
</tr>
</tbody>
</table>

- Gender
  - No. male (%)
    - Cohort 1A: 19 (47.5%)
    - Cohort 1B: 21 (52.5%)
    - Cohort 1C: 18 (45%)
    - Cohort 1D: 38 (47.5%)
    - Cohort 2A: 76 (63.3%)
    - Cohort 2B: 65 (54.2%)

- Ethnicity
  - Bambara
    - Cohort 1A: 12 (30.0%)
    - Cohort 1B: 13 (32.5%)
    - Cohort 1C: 14 (35.0%)
    - Cohort 1D: 38 (47.5%)
    - Cohort 2A: 47 (39.2%)
    - Cohort 2B: 38 (31.7%)
  - Mandika/Malinke
    - Cohort 1A: 17 (42.5%)
    - Cohort 1B: 14 (35.0%)
    - Cohort 1C: 10 (25.0%)
    - Cohort 1D: 22 (27.5%)
    - Cohort 2A: 29 (24.2%)
    - Cohort 2B: 43 (35.8%)
  - Fula/Peuhl
    - Cohort 1A: 5 (12.5%)
    - Cohort 1B: 5 (12.5%)
    - Cohort 1C: 8 (20.0%)
    - Cohort 1D: 7 (8.8%)
    - Cohort 2A: 13 (10.8%)
    - Cohort 2B: 13 (10.8%)
  - Sarahule/Sarakole
    - Cohort 1A: 1 (2.5%)
    - Cohort 1B: 3 (7.5%)
    - Cohort 1C: 4 (10.0%)
    - Cohort 1D: 2 (2.5%)
    - Cohort 2A: 9 (7.5%)
    - Cohort 2B: 5 (4.2%)
  - Other
    - Cohort 1A: 5 (12.5%)
    - Cohort 1B: 5 (12.5%)
    - Cohort 1C: 4 (10.0%)
    - Cohort 1D: 11 (13.7%)
    - Cohort 2A: 22 (18.3%)
    - Cohort 2B: 21 (17.5%)
**Study Design – Safety Review**

- **Step 1A**
  - 20 - 35 yrs
  - N = 40
  - ICSM review

- **Step 1B**
  - 5 - 9 yrs
  - N = 40
  - ICSM review

- **Step 1C**
  - 24 - 59 mon
  - N = 40
  - ICSM review

- **Step 1D**
  - 16 - 23 mon
  - N = 80
  - DSMB review

- **Step 2A**
  - 12 – 16 mon
  - N = 120
  - DSMB review

- **Step 2B**
  - 8 – 11 mon
  - N = 120
  - DSMB review

- **Step 3**
  - 12 – 14 wks
  - N = 180
  - ICSM review

- **Step 3**
  - 16 – 18 wks
  - N = 180
  - ICSM review

- **Step 4**
  - Prime 12 – 18 wks
  - Boost:
    - 9 mon OR
    - 12 mon OR
    - 15-17 mon
  - N = 456
  - DSMB review