Study design and initial data from a Phase 1 randomized controlled observer-blind, trial to evaluate the safety, reactogenicity and immunogenicity of a trivalent vaccine against invasive nontyphoidal *Salmonella* and typhoid fever in healthy adults in Europe

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NCT05480800
A vaccine against invasive nontyphoidal salmonellosis (iNTS) and typhoid fever: iNTS-TCV

Global (2019, all ages)

Typhoid fever:
- 110,029 deaths
- 9,237,225 cases

iNTS:
- 79,046 deaths
- 593,877 cases

Deaths by age

- <5 yr: 17%
- 5-14 yr: 43%
- ≥15 yr: 40%

Sub-Saharan Africa
- 18,704 deaths
- 1,237,347 cases
- 69,844 deaths
- 480,425 cases

South Asia
- 76,644 deaths
- 6,551,042 cases
- 5,058 deaths
- 56,931 cases

GBD 2019, IHME website accessed 11/2023
iNTS-TCV trivalent vaccine:
Combination of two technologies: GMMA + glycoconjugate

Vi-CRM$_{197}$ Drug Substance of a licensed vaccine, WHO PQ (Biological E Ltd)
Study Design

This is a phase 1/2a, observer-blind, randomized, controlled, two-stage, multi-country study to evaluate the safety, reactogenicity, and immune response of the trivalent vaccine against invasive nontyphoidal Salmonella (iNTS) and Typhoid Fever in healthy European and African adults.

- Planned enrolment: A total of 155 healthy adults 18–50 years of age will be randomized.
- 50 European adults were randomly assigned to 1 of the intervention groups in stage 1 while 105 African adults will be randomized in stage 2.
- Each participant will receive 2 interventions concomitantly in separate arms: iNTS-TCV and saline OR iNTS and TCV vaccines OR placebo/controls and saline.
- Each participant will receive a study intervention per arm on Day 1, Day 57 and Day 169. Approximately 13 months participation duration.
- Schedule selected based on number of doses expected to be immunogenic in target population for primary immunization (i.e. infants 6 weeks of age)
- The highest dose of the iNTS-TCV used in this trial was tested in a repeated-dose toxicology study in rabbits which showed good tolerance with no evidence of toxicity.
## Study Design Overview

### Stage 1 (Belgium)
- **Step 1**: 10 adults
  1. INTS-TCV low dose
  2. INTS-GMMA and TCV low doses
  3. Placebo_Step 1
- **Step 2**: 10 adults + 30 Adults
  4. INTS-TCV full dose_1
  5. INTS-GMMA and TCV full doses_1
  6. Placebo_Step 2

### Stage 2 (Malawi)
- **Stage 2**: 21 Adults
  7. INTS-TCV full dose_2
  8. INTS-GMMA and TCV full doses_2
  9. Control_Stage 2
- **Stage 2**: 84 Adults
  7. INTS-TCV full dose_2
  8. INTS-GMMA and TCV full doses_2
  9. Control_Stage 2

### Overview:
- **Screening**
  - Day -28 to Day -1
- **First Administration Phase**
  - Visit 1 (Day 1)
  - Visit 2 (Day 8)
  - Visit 3 (Day 29)
  - Visit 4 (Day 57)
  - Visit 5 (Day 64)
  - Visit 6 (Day 85)
  - Visit 7 (Day 169)
  - Visit 8 (Day 176)
  - Visit 9 (Day 197)
- **Second Administration Phase**
  - Visit 1 (Day 1)
  - Visit 2 (Day 8)
  - Visit 3 (Day 29)
  - Visit 4 (Day 57)
  - Visit 5 (Day 64)
  - Visit 6 (Day 85)
  - Visit 7 (Day 169)
  - Visit 8 (Day 176)
  - Visit 9 (Day 197)
- **Third Administration Phase**
  - Visit 1 (Day 1)
  - Visit 2 (Day 8)
  - Visit 3 (Day 29)
  - Visit 4 (Day 57)
  - Visit 5 (Day 64)
  - Visit 6 (Day 85)
  - Visit 7 (Day 169)
  - Visit 8 (Day 176)
  - Visit 9 (Day 197)

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**Interim Analysis**
- Long-term safety phone call at Day 337
- Safety phone calls/home visits on the day following 1st administration
- Reminder phone call on Day 4/home visits on Days 2-7 to fill in diary cards
- Unblinded Safety Evaluation

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*Participants receive the study interventions on consecutive days
**Participants receive the study interventions every 60 minutes

- Safety/immunogenicity blood draw
- Safety blood draw
- Immunogenicity blood draw
# Study Objectives and endpoints

## Primary Objective

<table>
<thead>
<tr>
<th>Objective</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>To evaluate the safety and reactogenicity of the iNTS-TCV vaccine in healthy European/African adults</td>
<td>Percentage of participants with</td>
</tr>
<tr>
<td></td>
<td>▪ solicited administration site and systemic events during 7 days after each study intervention administration</td>
</tr>
<tr>
<td></td>
<td>▪ unsolicited AEs during 28 days after each study intervention administration</td>
</tr>
<tr>
<td></td>
<td>▪ Serious AE</td>
</tr>
<tr>
<td></td>
<td>▪ AEs leading to withdrawal</td>
</tr>
<tr>
<td></td>
<td>▪ Deviations from ranges or baseline hematological, renal and hepatic panel test</td>
</tr>
</tbody>
</table>
Blinded Safety data from Phase 1
This presentation covers initial data from stage 1 of the study ongoing in Belgium, where 50 participants have been recruited (i.e. data up to 28 days after 2nd administration in the full dose group).

<table>
<thead>
<tr>
<th>Study Design Overview</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1 (10 adults)</strong>*</td>
</tr>
<tr>
<td>1. INTS-TCV low dose</td>
</tr>
<tr>
<td>2. INTS-GMMA and TCV low doses</td>
</tr>
<tr>
<td>3. Placebo_Step 1 (2:2:1)</td>
</tr>
<tr>
<td><strong>Stage 1 (Belgium)</strong></td>
</tr>
<tr>
<td><em><em>Step 2 (10 adults</em> + 10 Adults</em>*)**</td>
</tr>
<tr>
<td>4. INTS-TCV full dose_1</td>
</tr>
<tr>
<td>5. INTS-GMMA and TCV full doses_1</td>
</tr>
<tr>
<td>6. Placebo_Step 2 (2:2:1)</td>
</tr>
</tbody>
</table>

*Sentinel Participants receive the study interventions on consecutive days
**Participants receive the study interventions every 60 minutes

- Safety/immunogenicity blood draw
- Safety blood draw
- Immunogenicity blood draw
- Reminder phone call on Day 4/ home visits on Days 2-7 to fill in diary cards
- Unblinded Safety Evaluation
- Long-term safety phone call at Day 337
- Safety Phone calls/home visits on the day following 1st administration
### Summary of Demographic Characteristics (Exposed Set) - Blinded

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Parameter or Categories</th>
<th>Low Dose (N=10) Value or n(%)</th>
<th>Full Dose (N=40) Value or n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Female</td>
<td>7 (70.0)</td>
<td>29 (72.5)</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>3 (30.0)</td>
<td>11 (27.5)</td>
</tr>
<tr>
<td>Race</td>
<td>Other</td>
<td>-</td>
<td>2 (5.0)</td>
</tr>
<tr>
<td></td>
<td>White</td>
<td>10 (100.0)</td>
<td>38 (95.0)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>n</td>
<td>10</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>30.7</td>
<td>34.7</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>10.93</td>
<td>10.86</td>
</tr>
<tr>
<td></td>
<td>Minimum</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>28.5</td>
<td>36.0</td>
</tr>
<tr>
<td></td>
<td>Maximum</td>
<td>48</td>
<td>50</td>
</tr>
</tbody>
</table>
Solicited Events analysis - Blinded

Percentage of participants reporting at least one solicited event

- **Low Dose (N=10)**
  - Any Administration Site: 30.0%
  - Systemic: 30.0%
  - Any Grade 3: 10.0%

- **Full Dose (N=40)**
  - Any Administration Site: 35.0%
  - Systemic: 32.5%
  - Any Grade 3: 7.5%

Legend:
- Blue: Any
- Green: Administration Site
- Red: Systemic
- Black: Any Grade 3
- Light blue: Administration Site Grade 3
- Maroon: Systemic Grade 3
Solicited Administrative Site Events - Blinded

Percentage of participants reporting solicited administration site events

<table>
<thead>
<tr>
<th>Event</th>
<th>Any</th>
<th>Grade 3</th>
<th>Redness</th>
<th>Any</th>
<th>Grade 3</th>
<th>Swelling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>100.0%</td>
<td>30.0%</td>
<td>15.0%</td>
<td>10.0%</td>
<td>30.0%</td>
<td>15.0%</td>
</tr>
<tr>
<td>Grade 3</td>
<td>87.5%</td>
<td>15.0%</td>
<td>30.0%</td>
<td>10.0%</td>
<td>17.5%</td>
<td>15.0%</td>
</tr>
</tbody>
</table>

Legend: Low Dose (N=10) | Full Dose (N=40)
Systemic Solicited Events - Blinded

Percentage of participants reporting solicited systemic events

<table>
<thead>
<tr>
<th>Event</th>
<th>Low Dose (N=10)</th>
<th>Full Dose (N=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthralgia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>30.0%</td>
<td>60.0%</td>
</tr>
<tr>
<td>Any</td>
<td>17.5%</td>
<td>60.0%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0.0%</td>
<td>60.0%</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0.0%</td>
<td>60.0%</td>
</tr>
<tr>
<td>Any</td>
<td>2.5%</td>
<td>10.0%</td>
</tr>
<tr>
<td>Fever</td>
<td>0.0%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0.0%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Any</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Headache</td>
<td>70.0%</td>
<td>70.0%</td>
</tr>
<tr>
<td>Grade 3</td>
<td>10.0%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Any</td>
<td>10.0%</td>
<td>40.0%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>42.5%</td>
<td>42.5%</td>
</tr>
<tr>
<td>Grade 3</td>
<td>2.5%</td>
<td>2.5%</td>
</tr>
</tbody>
</table>

Legend: Low Dose (N=10) | Full Dose (N=40)
Unsolicited Adverse Events - Blinded

After all participants received at least 2 doses of study interventions _ comparators

Low Dose group (N=10):
• At least one event reported by 80% of subjects participants.
• 60% reported at least one event considered related to vaccination by the INV
• No Grade 3 reported.
• Overall, most frequent SOC (system organ class) affected were «Infections and infestations» (50% of participants) and «Musculoskeletal and connective tissue disorders” (40% of participants).

Full Dose group (N=40):
• At least one event reported by 90% of subjects participants.
• 50% of subjects reported at least one event considered related to vaccination by the INV
• Overall, most frequent SOC were «Infections and infestations» (42.5% of participants) and «General disorders and administration site Conditions” (37.5% of participants).
• GR3 events were reported in 12.5% of subjects participants.
Conclusions

- After at least two administrations with the low or full doses or controls, the majority of adverse events (AEs) observed are of mild to moderate intensity.
- No safety concerns are currently identified from the analysis of solicited, unsolicited AE events and Safety lab test results
  - No SAE considered related to vaccination reported
  - No AE leading to withdrawal
  - Injection site pain is the most frequent event reported in both steps, consistent with other GMMA studies.
  - Myalgia, fatigue and headache are the most frequent systemic solicited AEs
  - Severe unsolicited AEs considered related to vaccination were reported in 2 subjects overall.
  - Safety lab test results: most laboratory results were within normal reference ranges and there were no clinically significant changes from normal

Based on available safety data, clinical development has progressed into healthy adults in an endemic African country, to further assess safety and immunogenicity of the iNTS-TCV vaccine.
Acknowledgements

• iNTS Project team at GVGH and GSK
• All site staff at Center for Evaluation of Vaccination Belgium
• All study participants and their families
Acknowledgements

GSK Vaccines Institute for Global Health (GVGH) – Global Health Vaccines R&D team (past and present staff)

Research reported in this presentation is supported by CARB-X. CARB-X’s funding for this project is provided in part with federal funds from the U.S. Department of Health and Human Services Administration for Strategic Preparedness and Response Biomedical Advanced Research and Development Authority; under agreement number: 75A50122C00028, and by awards from Wellcome (WT224842), the UK Global Antimicrobial Resistance Innovation Fund (GAMRIF) funded by the UK Government Department of Health and Social Care (DHSC), and the Bill & Melinda Gates Foundation. The content of this presentation is solely the responsibility of the authors and does not necessarily represent the official views of CARB-X or any of its funders.

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Declaration and conflicts

KW has nothing to disclose. YSI, ALDP, ASB, GLC, OR, BG, CC, RLG, VC, UNN, RC and AKA are GSK employees. GLC, OR, RLG, VC, UNN, RCA, and AKA hold GSK shares or stock options.
Thank you