Study design and initial data from a Phase 1 randomised controlled observer-blind, trial to evaluate the safety, reactogenicity and immunogenicity of a bivalent vaccine against *Salmonella* Typhi and *Salmonella* Paratyphi A in healthy adults in Europe (NCT05613205)

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Disclosures and funding statement

• UNN, ES, ASC, GLC, ASB, ISDR, MC, LM, SR, VC, OR and AKA are GSK employees. UNN, GLC, ISDR, MC, SR, VC, OR, and AKA hold GSK shares or stock options.

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• IDC acts as principal investigator for vaccine trials conducted on behalf of the University of Antwerp, for which the University obtains research grants from vaccine manufacturers. IDC receives no personal remuneration for this work. ES, M-AG have nothing to declare.
Despite improved sociosanitary conditions in the last decade, enteric fever remains a major cause of disability and death.

There is a trend of increased incidence of *S. Paratyphi* A in parts of Asia, estimated as ~35% of cases in India and Nepal and >60% of enteric fever in China, with a similar trend towards rising antimicrobial resistance.

We present the interim safety results from a first-time-in-human (FTIH) study aimed to evaluate the safety and immunogenicity profile of a novel Typhoid and Paratyphoid A conjugate vaccine (bivalent), aimed to prevent both typhoid and paratyphoid enteric fever in infants and older age groups.
Antigen Description

![Diagram showing antigen conjugation and the formation of a bivalent TCV (Vi-CRM\textsubscript{197} + O:2-CRM\textsubscript{197})](diagram.png)
### Protocol Title:
A Phase I, observer-blind, randomised, controlled, single-centre study to evaluate the safety, reactogenicity, and immune responses to an adjuvanted and non-adjuvanted conjugate vaccine against *Salmonella* Typhi and *Salmonella* Paratyphi A in healthy adults 18 – 50 years of age in Europe

### Rationale for Study:
First time in Human (FIH) Clinical Trial to characterize safety and immunogenicity profile of the candidate vaccine

### Description of study:
96 healthy adults received either a high or lower dose of the candidate bivalent vaccine with or without alum adjuvant or active comparators.

### Primary Objective:
Evaluate the safety profile of the fVi-CRM$_{97}$+O:2-CRM$_{97}$ vaccine with and without a adjuvant

### Secondary Objectives:
1. Evaluate the long-term safety profile of the fVi-CRM$_{97}$+O:2-CRM$_{97}$ vaccine with and without adjuvant
2. Evaluate the immunogenicity profile of typhoid and paratyphoid A components of fVi-CRM$_{97}$+O:2-CRM$_{97}$ vaccine with and without a adjuvant, using ELISA assay
3. Evaluate the seroresponse rate to the typhoid and paratyphoid A components of the fVi-CRM$_{97}$+O:2-CRM$_{97}$ vaccine, with and without a adjuvant

### Investigational Products:

<table>
<thead>
<tr>
<th>• Two dose levels of Typhi/Paratyphi A vaccine with and without adjuvant are tested in the study:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 5µg/5µg dose (low dose – by fractional dosing)</td>
</tr>
<tr>
<td>• 5µg/5µg dose with aluminum hydroxide (low dose adjuvanted – by fractional dosing)</td>
</tr>
<tr>
<td>• 25µg/25µg dose (full dose)</td>
</tr>
<tr>
<td>• 25µg/25µg dose with aluminum hydroxide (full dose adjuvanted)</td>
</tr>
</tbody>
</table>

- Manufactured by Biological E Ltd. (Bio E, India)
- Manufactured by Sanofi Pasteur
- Manufactured by GSK

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Interim analysis results

Subject disposition and inclusion in Per Protocol Set

145 Assessed for eligibility
49 Excluded
96 Randomised

12 Low dose
12 Low Dose + Alum
24 Control
24 Full dose + Alum
24 Full dose

1 Inclusion/Exclusion criteria
11 PPS
24 PPS
24 PPS
24 PPS
21 PPS

1 Visit schedule
2 No serology available

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## Interim analysis results

### Demographic characteristics of Exposed Population

<table>
<thead>
<tr>
<th></th>
<th>Low Dose (N=12)</th>
<th>Low Dose + Alum (N=12)</th>
<th>Full Dose (N=24)</th>
<th>Full Dose + Alum (N=24)</th>
<th>Typhim Vi (N=24)</th>
<th>All Participants (N=96)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>n (%)</td>
<td>1 (8.3)</td>
<td>6 (50.0)</td>
<td>10 (41.7)</td>
<td>7 (29.2)</td>
<td>6 (25.0)</td>
</tr>
<tr>
<td>Female</td>
<td>n (%)</td>
<td>11 (91.7)</td>
<td>6 (50.0)</td>
<td>14 (58.3)</td>
<td>17 (70.8)</td>
<td>18 (75.0)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>n</td>
<td>12</td>
<td>12</td>
<td>24</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>31.9</td>
<td>31.8</td>
<td>27.0</td>
<td>27.1</td>
<td>30.7</td>
</tr>
<tr>
<td>Minimum</td>
<td></td>
<td>20</td>
<td>20</td>
<td>18</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Maximum</td>
<td></td>
<td>47</td>
<td>49</td>
<td>49</td>
<td>46</td>
<td>50</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td>n (%)</td>
<td>12 (100.0)</td>
<td>12 (100.0)</td>
<td>24 (100.0)</td>
<td>24 (100.0)</td>
<td>24 (100.0)</td>
</tr>
<tr>
<td>White</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Country</td>
<td>n (%)</td>
<td>12 (100.0)</td>
<td>12 (100.0)</td>
<td>24 (100.0)</td>
<td>24 (100.0)</td>
<td>24 (100.0)</td>
</tr>
<tr>
<td>Belgium</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

n / % = number/ percentage of participants in each category; Source: Table 14.16
**Interim analysis results**

**Solicited Events analysis – 7 days post dose 1**

Proportion of participants reporting at least one solicited event

- **Low Dose (N=12)**:
  - Any: 25.0%
  - Systemic: 8.3%
  - Administartion Site: 8.3%
  - Any Grade 3: 58.3%
  - Systemic Grade 3: 58.3%
  - Administartion Site Grade 3: 91.7%

- **Low Dose+Alum (N=12)**:
  - Any: 25.0%
  - Systemic: 8.3%
  - Administartion Site: 8.3%
  - Any Grade 3: 58.3%
  - Systemic Grade 3: 58.3%
  - Administartion Site Grade 3: 91.7%

- **Full Dose (N=23)**:
  - Any: 73.9%
  - Systemic: 70.8%
  - Administartion Site: 70.8%
  - Any Grade 3: 87.0%
  - Systemic Grade 3: 91.7%
  - Administartion Site Grade 3: 95.7%

- **Full Dose+Alum (N=24)**:
  - Any: 73.9%
  - Systemic: 70.8%
  - Administartion Site: 70.8%
  - Any Grade 3: 87.0%
  - Systemic Grade 3: 91.7%
  - Administartion Site Grade 3: 95.7%

- **TYPHIM Vi (N=24)**:
  - Any: 73.9%
  - Systemic: 70.8%
  - Administartion Site: 70.8%
  - Any Grade 3: 87.0%
  - Systemic Grade 3: 91.7%
  - Administartion Site Grade 3: 95.7%
Interim Analysis results
Solicited Events analysis – 7 days post dose 1

Proportion of participants reporting systemic solicited events

Proportion of participants reporting administration site events

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Interim analysis results

Unsolicited Adverse Events analysis – 28 days post dose 1

- No Serious Adverse Events (SAEs)
- No Adverse Events (AEs) leading to study/treatment discontinuation
- No Deaths
Conclusions

• There were no SAEs, AEs leading to withdrawal from the study or Interventional Product discontinuation up to 28 days after the first study intervention administration in all groups.

• Pain was the most frequently reported solicited administration site event, reported at a similar frequency for all groups except for the Low Dose group without alum which showed a lower frequency. Overall, one grade 3 pain was reported in the Full Dose group with alum.

• Solicited systemic events were reported at a similar frequency for the Full Dose groups and the Control group. There was a higher frequency of grade 3 events (3) in the Full Dose + Alum group.

• Unsolicited AEs were reported with a similar frequency across the groups, with a higher frequency of related severe AEs in the Alum groups (8.3%).
Acknowledgements

- Enteric Fever Project team at GVGH and GSK
- All site staff at Center for Evaluation of Vaccination Belgium
- All study participants and their families
Back up slides
Solicited & Unsolicited Adverse events analysis – 28 days post dose 1

% of subjects reporting at least one AE

- Low Dose (N=12)
- Low Dose+Alum (N=12)
- Full Dose (N=23)
- Full Dose+Alum (N=24)
- TYMPIM VI (N=24)
# Unsolicited Adverse events analysis –28 days post dose 1

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Blood and lymphatic system disorders</th>
<th>Gastrointestinal disorders</th>
<th>General disorders and administration site conditions</th>
<th>Infections and infestations</th>
<th>Investigations</th>
<th>Musculoskeletal and connective tissue disorders</th>
<th>Nervous system disorders</th>
<th>Reproductive system and breast disorders</th>
<th>Respiratory, thoracic and mediastinal disorders</th>
<th>Skin and subcutaneous tissue disorders</th>
<th>Vascular disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Dose (N=12)</td>
<td>8.3%</td>
<td>8.3%</td>
<td></td>
<td></td>
<td></td>
<td>8.3%</td>
<td>16.7%</td>
<td>8.3%</td>
<td>8.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Dose+Alum (N=12)</td>
<td>16.7%</td>
<td>16.7%</td>
<td></td>
<td></td>
<td></td>
<td>8.3%/8.3%</td>
<td>8.3%</td>
<td>8.3%</td>
<td>8.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full Dose (N=23)</td>
<td>4.3%</td>
<td>4.3%</td>
<td>13.0%</td>
<td></td>
<td>8.7%/4.3%</td>
<td>13.0%</td>
<td>4.3%</td>
<td>4.3%</td>
<td>4.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full Dose+Alum (N=24)</td>
<td>4.2%</td>
<td>4.2%</td>
<td>12.5%/8.3%</td>
<td></td>
<td>4.2%</td>
<td>4.2%</td>
<td>4.2%</td>
<td>4.2%</td>
<td>4.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TYMPIM VI (N=24)</td>
<td>8.3%</td>
<td></td>
<td></td>
<td></td>
<td>4.2%</td>
<td>4.2%</td>
<td>4.2%</td>
<td>4.2%</td>
<td>4.2%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Unsolicited Related AEs/Related Grade 3**

- Hemoglobin decrease
- Migraine
Rate of Concomitant Medication use – 28 days post dose 1

<table>
<thead>
<tr>
<th></th>
<th>Low dose without alum (%)</th>
<th>Low dose with alum (%)</th>
<th>Full dose without alum (%)</th>
<th>Full dose with alum (%)</th>
<th>Typhim Vi (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>12</td>
<td>12</td>
<td>24</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Any Medication</td>
<td>91.7</td>
<td>75.0</td>
<td>79.2</td>
<td>79.2</td>
<td>83.3</td>
</tr>
<tr>
<td>Antipyretic</td>
<td>41.7</td>
<td>41.7</td>
<td>33.3</td>
<td>45.8</td>
<td>66.7</td>
</tr>
<tr>
<td>Prophylactic Antipyretic</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>8.3</td>
<td>8.3</td>
<td>-</td>
<td>12.5</td>
<td>8.3</td>
</tr>
</tbody>
</table>
### Safety Lab results summary

<table>
<thead>
<tr>
<th></th>
<th>Low dose without alum</th>
<th>Low dose with alum</th>
<th>Full dose without alum</th>
<th>Full dose with alum</th>
<th>Typhim VI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>12</td>
<td>12</td>
<td>24</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td><strong>Grade 1 abnormalities</strong></td>
<td>4</td>
<td>3</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Grade 1 Hb change from baseline</strong></td>
<td>8</td>
<td>6</td>
<td>14</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td><strong>Grade 2 Hb change from baseline</strong></td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Grade 3 or above Hb change from baseline</strong></td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

- No other grade 2 abnormalities reported
- No other grade 3 or above abnormalities reported