Preliminary results from an oral vaccine in the Paratyphoid Human Challenge Model

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S. Paratyphi A – unmet need for vaccines

3.8 million cases
~30% of enteric fever

Stanway et al, Lancet ID, 2019
CHIM is a valuable method to assess efficacy of S. Paratyphi A vaccine candidates

Demonstration of vaccine efficacy against S. Paratyphi A is considered difficult, as a low attack rate means that an efficacy study will need around 100,000 – 250,000 participants. A CHIM for S. Paratyphi A has been developed and can potentially be a valuable way to assess the efficacy of the current paratyphoid vaccine candidates. Licensure of bivalent typhoid-paratyphoid vaccines can be supported on the basis of Phase II efficacy (from CHIM) and field immunogenicity for the S. Paratyphi A component to demonstrate non-inferiority (on immunogenicity) to licensed typhoid conjugate vaccines. Such an accelerated pathway would likely require post-licensure effectiveness studies.

Updated April 30, 2022
**VASP trial to assess CVD 1902**

- **Testing efficacy of CVD 1902, live attenuated vaccine** against SPA
- **Observer-participant blinded randomised, placebo-controlled trial**

<table>
<thead>
<tr>
<th>Paratyphoid fever is diagnosed if ANY of the following apply</th>
</tr>
</thead>
<tbody>
<tr>
<td>A positive blood culture for S. Paratyphi A from 72 hours post-challenge</td>
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<tr>
<td>A positive blood culture for S. Paratyphi A within 72 hours post-challenge, with one or more signs/symptoms of paratyphoid infection (such as recorded temperature ≥38.0°C)</td>
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<tr>
<td>Persistent positive blood cultures (two or more blood cultures taken at least 4 hours apart) for S. Paratyphi A within 72 hours post-challenge.</td>
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<tr>
<td>Oral temperature ≥38.0°C persisting for 12 hours</td>
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</table>
Objectives

**PRIMARY**

• Determine relative protection of 2 doses of CVD 1902 vs placebo

**SECONDARY**

• Compare clinical and laboratory features of host response following challenge in vaccinated vs placebo
• Compare host immune response following vaccination in those vaccinated vs placebo
• Compare host immune response following challenge in those vaccinated vs placebo
• To assess safety and tolerability of CVD 1902
• To investigate immunological correlates of protection for S. Paratyphi A

Sample size – 66-76 participants
Strict inclusion/exclusion criteria

- Healthy adult volunteers (18-55)
  - Gallstones excluded

- Not putting others at risk
  - Occupation
  - Household contacts

- Not affect study outcomes
  - Prior challenge/infection

https://radiopaedia.org/cases/gallstones-1
Recruitment completed

Study start

21 enrolled

Expanded to 5 additional sites

72 enrolled

Study paused

2022

2023

Enrolled / received first vaccination = 72

Received second vaccination = 55

Been challenged = 52

Completed challenge = 42

Reached D90 = 33

Completed 1 year follow-up = 18
### Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (%) or median (range)</th>
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<tbody>
<tr>
<td><strong>Age, median (range)</strong></td>
<td>31.5 (20-54)</td>
</tr>
<tr>
<td><strong>Sex at birth</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>33 (46%)</td>
</tr>
<tr>
<td>Male</td>
<td>39 (54%)</td>
</tr>
<tr>
<td><strong>Ethnic origin</strong></td>
<td></td>
</tr>
<tr>
<td>White British</td>
<td>51 (71%)</td>
</tr>
<tr>
<td>White other</td>
<td>9 (12.5%)</td>
</tr>
<tr>
<td>Mixed</td>
<td>6 (8%)</td>
</tr>
<tr>
<td>Asian</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (4%)</td>
</tr>
<tr>
<td><strong>Occupation</strong></td>
<td></td>
</tr>
<tr>
<td>Student</td>
<td>20 (28%)</td>
</tr>
</tbody>
</table>
CVD 1902 appears to be well-tolerated

Maximum severity of solicited symptoms experienced by participant during week following *prime* vaccination

Maximum severity of solicited symptoms experienced by participant during week following *boost* vaccination
Significant rise in SBA titres following CVD 1902 vaccination
Paratyphoid A in CHIM causes predominantly mild disease

Current attack rate 50%
No hospital admissions
No severe disease

Maximum severity of symptoms experienced by diagnosed participants in the 21 days following challenge

Severity:
- mild
- moderate
- severe
Majority of diagnoses are microbiological

90% diagnoses microbiological

Fevers in 29%

Median day of diagnosis = D8

Median days of bacteraemia = 3
Summary

• CVD 1902 appears safe, well-tolerated & immunogenic

• S. Paratyphi A in CHIM model is usually mild

• Success of first multi-site enteric challenge model
Next steps

- Study completion 2024
- Efficacy data presentation/publication mid-2024
- Towards bivalent vaccination
- Immunology & sequencing work investigating correlates of protection
- Validated model for testing of other paratyphoid vaccine candidates
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