



Clinical trial results:

Understanding typhoid disease after vaccination: a single centre, randomised, double-blind, placebo-controlled study to evaluate M01ZH09 in a healthy adult challenge model, using Ty21a vaccine as a positive control.

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2011-000381-35 |
| Trial protocol | GB |
| Global end of trial date | 06 May 2022 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 21 May 2023 |
| First version publication date | 21 May 2023 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | OVG 2011/02 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01405521 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | University of Oxford, Research Governance, Ethics & Assurance Team (RGEA) |
| Sponsor organisation address | Boundary Brook House, Oxford, United Kingdom, OX3 7GB |
| Public contact | Andrew J Pollard, University of Oxford, +44 1865611400, andrew.pollard@paediatrics.ox.ac.uk |
| Scientific contact | Andrew J Pollard, University of Oxford, +44 1865611400, andrew.pollard@paediatrics.ox.ac.uk |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 17 August 2016 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 06 May 2022 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Primary objective: To determine the relative protective effect of M01ZH09 vaccine compared to placebo in a healthy adult typhoid challenge model, using the licensed Ty21a vaccine as a positive control

Secondary objectives

- 1) To compare the clinical and laboratory features of the host responses following S. Typhi challenge in participants vaccinated with M01ZH09, placebo or Ty21a
- 2) To compare the immune response following M01ZH09, placebo or Ty21a vaccination and to relate these responses to the protective effect of vaccination during subsequent challenge
- 3) To assess the safety and tolerability of M01ZH09 and to compare to Ty21a and placebo
- 4) To develop diagnostic methods for S. Typhi infection
- 5) To explore the variation in genomic response to vaccination with M01ZH09, placebo and Ty21A, and subsequent challenge
- 6) To confirm the scientific integrity of the demonstrated protective effect of vaccination in the challenge model
- 7) To gather information on participant experience

Protection of trial subjects:

The trial staff ensured that the participants' anonymity was maintained.

The general risks to the participants were associated with venepuncture, use of the IMP (M01ZH09 vaccine) and challenge with live typhoid-causing bacteria. In view of the low infectivity of S. Typhi without gastric acid suppression and the general level of hygiene and sanitation in the UK, secondary transmission of either S. Typhi vaccine strains or challenge strain to household or other close contacts was highly unlikely.

Participants were instructed to complete a Diary Card, recording oral temperatures twice-daily and describing any symptoms or usage of any medications daily. The diary card was completed from point of first vaccination for 7 days. At this stage the participant was asked to document additional details regarding any visits seeking medical advice. The Diary Card was reviewed when the participants attended for the post-vaccination visit.

Participants were issued with a Medic Alert-type card containing information including the antibiotic sensitivity of the S. Typhi strain, study doctor contact details and instruction for the research team to be contacted immediately in the event of illness/accident.

Participants did not have to remain on site between assessments but a rest room was provided which they could use if they wished.

Participants had access to a study physician 24-hours a day, from the time of vaccination until they were deemed to be clear of S. Typhi infection. Following challenge, participants were encouraged to contact one of the study investigators on the 24-hour emergency telephone number if they developed symptoms of typhoid between the regular reviews, or when their temperature exceeded 38C. The investigators considered extra clinical reviews if the participants symptoms were moderate or severe, or at their request. Severity of symptoms was assessed and if participants were unwell as a result of S. Typhi infection, they were visited in their homes.

Background therapy:

Four weeks after completion of the immunisation or placebo course, participants were challenged with Salmonella Typhi (Quail's strain) at an infective dose ($1-5 \times 10^4$ CFU) previously demonstrated to give the desired clinical/laboratory attack rate.

Evidence for comparator:

There are three vaccines currently licensed for the prevention of typhoid fever by active immunisation. These are:

- 1) The inactivated whole-cell vaccine, which is immunogenic in all age groups but also highly reactogenic, making it unpopular for widespread use as a control measure. It is no longer used.

2) The virulence factor capsular polysaccharide (ViPS) vaccine. ViPS does not generate immunological memory, its effect is not boosted by repeated vaccination and is also non-immunogenic in children under 2 years. ViPS vaccines are with only moderately efficacy and with limited efficacy duration.

3) Live attenuated oral vaccine Ty21a stimulates local mucosal immunity within the gut as well as systemic cell-mediated immunity and antibody responses following oral administration. There are extensive safety data available for Ty21a demonstrating excellent tolerability; it is the only currently licensed oral vaccine for the prevention of typhoid fever. Limitations include the multiple dosages required for full immunogenicity and efficacy to occur. Similar to ViPS vaccine, the Ty21a vaccine is only moderately efficacious.

Currently available vaccines are limited in their efficacy and cannot be used in young children. Novel vaccines with improved efficacy that can be given as a single dose to all age groups, including young children, are needed to reduce the morbidity and mortality seen with typhoid fever.

The M01ZH09 vaccine is a live attenuated S. Typhi vaccine based on the parent Ty2 strain containing two independently attenuating gene deletions, preventing bacterial growth and systemic spread. The safety and immunogenicity of M01ZH09 has been studied in six trials. It is given as a single dose and has also demonstrated immunogenicity and acceptability when used in children aged 5 to 14 years.

In this trial, we used M01ZH09 vaccine to investigate correlates of protection in a bacterial challenge model. Ty21a vaccine was used as a positive control.

| | |
|---|------------------|
| Actual start date of recruitment | 28 November 2011 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 99 |
| Worldwide total number of subjects | 99 |
| EEA total number of subjects | 0 |

Notes:

Subjects enrolled per age group

| | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 99 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled and randomised to the study arms between 18 November 2011 and 27 June 2012.

Adult participants were recruited by advertising and by providing an information booklet with detailed information about the study. After expression of interest was received, potential participants were contacted by the study team.

Pre-assignment

Screening details:

1371 responses, 710 Yes responses (269 declined participation, 287 excluded prior screening)

154 medical screening

Reasons for exclusions:

10 declined further participation

26 health concerns

7 previous typhoid vaccination

1 unavailable for visits

4 other

99 were enrolled and randomised

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Blinding implementation details:

The M01ZH09/vaccine placebo arm was double blinded, such that neither the investigator nor the participant knew which vaccine had been given/received as a single dose. The allocation of participants within the M01ZH09/ placebo arm to each treatment was by means of blinded packaging containing either M01ZH09 or placebo, in a 1:1 distribution.

Participants randomised to the positive control arm, received open-label Ty21a vaccine as 3 doses.

Arms

| | |
|--|---|
| Are arms mutually exclusive? | Yes |
| Arm title | Group 1: M01ZH09 vaccine |
| Arm description: | |
| 1 dose, oral; 28 days pre-challenge | |
| Arm type | Experimental |
| Investigational medicinal product name | Emergent BioSolutions live attenuated oral vaccine containing Salmonella enterica serovar Typhi Ty2 (aroC- ssaV-) ZH9 (M01ZH09) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for oral suspension |
| Routes of administration | Oral use |

Dosage and administration details:

1x10¹⁰ cfu suspended in sodium bicarbonate prior to oral ingestion. Contents of glass vial(s) containing 0.2-1.7x10¹⁰ cfu in M9S basal medium plus 10% (w/v) sucrose reconstituted in sodium bicarbonate solution, defined volume containing 1x10¹⁰ cfu removed to administration solution.

| | |
|-------------------------------------|------------------|
| Arm title | Group 2: placebo |
| Arm description: | |
| 1 dose, oral; 28 days pre-challenge | |
| Arm type | Placebo |

| | |
|--|---|
| Investigational medicinal product name | Emergent BioSolutions M01ZH09 vaccine-placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for oral suspension |
| Routes of administration | Oral use |
| Dosage and administration details: M9S basal medium plus 10% (w/v) sucrose reconstituted in sodium bicarbonate solution | |
| Arm title | Group 3: Ty21a vaccine |

Arm description:

3 doses, oral; 32, 30 and 28 days pre-challenge

| | |
|--|--|
| Arm type | Active comparator |
| Investigational medicinal product name | Crucell live attenuated oral vaccine containing Salmonella enterica serovar Typhi Ty21a (Vivotif®) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

not less than 2 x 10⁹ viable cells per enteric-coated capsule, taken on day 1, 3 and 5 by oral ingestion

| Number of subjects in period 1 | Group 1: M01ZH09 vaccine | Group 2: placebo | Group 3: Ty21a vaccine |
|---|--------------------------|------------------|------------------------|
| Started | 33 | 33 | 33 |
| Completed | 16 | 20 | 16 |
| Not completed | 17 | 13 | 17 |
| Consent withdrawn by subject | 7 | 6 | 10 |
| Not able to comply with study requirements | - | - | 1 |
| Travelling overseas | 1 | - | - |
| Time commitments | - | 1 | - |
| Withdrawal - participating in another trial | - | 1 | - |
| Lost to follow-up | 6 | 2 | 3 |
| Vomited post challenge | 1 | - | - |
| Moved away from area/ overseas | 2 | 3 | 3 |

Baseline characteristics

Reporting groups

| | |
|---|--------------------------|
| Reporting group title | Group 1: M01ZH09 vaccine |
| Reporting group description: 1 dose, oral; 28 days pre-challenge | |
| Reporting group title | Group 2: placebo |
| Reporting group description: 1 dose, oral; 28 days pre-challenge | |
| Reporting group title | Group 3: Ty21a vaccine |
| Reporting group description: 3 doses, oral; 32, 30 and 28 days pre-challenge | |

| Reporting group values | Group 1: M01ZH09 vaccine | Group 2: placebo | Group 3: Ty21a vaccine |
|--|--------------------------|------------------|------------------------|
| Number of subjects | 33 | 33 | 33 |
| Age categorical | | | |
| Age of participants in years | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 33 | 33 | 33 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous | | | |
| Units: years | | | |
| median | 24 | 23 | 25 |
| inter-quartile range (Q1-Q3) | 21 to 43 | 21 to 39 | 22 to 31 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 11 | 14 | 10 |
| Male | 22 | 19 | 23 |

| Reporting group values | Total | | |
|--|-------|--|--|
| Number of subjects | 99 | | |
| Age categorical | | | |
| Age of participants in years | | | |
| Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | | |
| Newborns (0-27 days) | 0 | | |
| Infants and toddlers (28 days-23 months) | 0 | | |
| Children (2-11 years) | 0 | | |

| | | | |
|------------------------------|----|--|--|
| Adolescents (12-17 years) | 0 | | |
| Adults (18-64 years) | 99 | | |
| From 65-84 years | 0 | | |
| 85 years and over | 0 | | |
| Age continuous | | | |
| Units: years | | | |
| median | | | |
| inter-quartile range (Q1-Q3) | - | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 35 | | |
| Male | 64 | | |

End points

End points reporting groups

| | |
|---|--------------------------|
| Reporting group title | Group 1: M01ZH09 vaccine |
| Reporting group description: | |
| 1 dose, oral; 28 days pre-challenge | |
| Reporting group title | Group 2: placebo |
| Reporting group description: | |
| 1 dose, oral; 28 days pre-challenge | |
| Reporting group title | Group 3: Ty21a vaccine |
| Reporting group description: | |
| 3 doses, oral; 32, 30 and 28 days pre-challenge | |

Primary: Typhoid Diagnosis

| | |
|---|-------------------|
| End point title | Typhoid Diagnosis |
| End point description: | |
| Clinical of Microbiological definition of typhoid diagnosis | |
| End point type | Primary |
| End point timeframe: | |
| During 14 day challenge period | |

| End point values | Group 1: M01ZH09 vaccine | Group 2: placebo | Group 3: Ty21a vaccine | |
|-----------------------------|--------------------------------|---------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 31 | 30 | 30 | |
| Units: Participants | 18 | 20 | 13 | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Vaccine Efficacy M01ZH09 vs Placebo |
| Comparison groups | Group 2: placebo v Group 1: M01ZH09 vaccine |
| Number of subjects included in analysis | 61 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Vaccine Efficacy |
| Point estimate | 13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -29 |
| upper limit | 41 |

| | |
|---|---|
| Statistical analysis title | Vaccine Efficacy: Ty21a vs placebo |
| Comparison groups | Group 3: Ty21a vaccine v Group 2: placebo |
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Vaccine Efficacy |
| Point estimate | 35 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5 |
| upper limit | 60 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Solicited adverse events: first 7 days after vaccination or first 21 days after challenge

SAEs: whole duration of the study

Adverse event reporting additional description:

Frequency of solicited adverse events during the first 21 days after challenge, according to vaccine group allocation. The 'classical triad' of typhoid fever presentation: fever, headache and abdominal pain are reported here. Full report of the solicited adverse events: https://doi.org/10.1371/journal.pntd.0004926_S1_Table

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|--------------------|----------|
| Dictionary name | Protocol |
| Dictionary version | 5.1 |

Reporting groups

| | |
|-----------------------|--------------------------|
| Reporting group title | Group 1: M01ZH09 vaccine |
|-----------------------|--------------------------|

Reporting group description:

1 dose, oral; 28 days pre-challenge

| | |
|-----------------------|------------------|
| Reporting group title | Group 2: placebo |
|-----------------------|------------------|

Reporting group description:

1 dose, oral; 28 days pre-challenge

| | |
|-----------------------|------------------------|
| Reporting group title | Group 3: Ty21a vaccine |
|-----------------------|------------------------|

Reporting group description:

3 doses, oral; 32, 30 and 28 days pre-challenge

| Serious adverse events | Group 1: M01ZH09 vaccine | Group 2: placebo | Group 3: Ty21a vaccine |
|---|--------------------------|------------------|------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 4 / 30 (13.33%) | 1 / 30 (3.33%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Femur and ankle injury following fall in high heels | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 30 (0.00%) | 1 / 30 (3.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nasal Fracture | | | |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 30 (0.00%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Concussion | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 30 (3.33%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Mood alteration, depression symptoms | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 30 (3.33%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Febrile illness | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 30 (3.33%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Drug induced liver injury | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 30 (3.33%) | 0 / 30 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | Group 1: M01ZH09 vaccine | Group 2: placebo | Group 3: Ty21a vaccine |
|---|--------------------------------------|-------------------|------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 32 / 32 (100.00%) | 30 / 30 (100.00%) | 30 / 30 (100.00%) |
| General disorders and administration site conditions | | | |
| Headache | | | |
| subjects affected / exposed | 23 / 32 (71.88%) | 27 / 30 (90.00%) | 19 / 30 (63.33%) |
| occurrences (all) | 23 | 27 | 19 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 18 / 32 (56.25%) | 18 / 30 (60.00%) | 14 / 30 (46.67%) |
| occurrences (all) | 18 | 18 | 14 |
| Infections and infestations | | | |
| Fever | Additional description: Fever (>38°) | | |

| | | | |
|-----------------------------|------------------|------------------|-----------------|
| subjects affected / exposed | 14 / 32 (43.75%) | 16 / 30 (53.33%) | 9 / 30 (30.00%) |
| occurrences (all) | 14 | 16 | 9 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 04 October 2011 | <ol style="list-style-type: none">1. Update of findings from OVG 2009/10.2. Addition of study flowchart (figure 1).3. Clarification of Pregnancy section (3.4.7) and addition of figure 2.4. Alteration of randomisation method to sealed envelopes.5. Removal of medical examination from visits after day 28.6. Clarification of typhoid fever diagnosis in participants who are bacteraemic and symptomatic before day 5 following challenge.7. Clarification of method to be used to ensure accurate IMP vaccine dose given.8. Alteration of formatting and clarification of adverse event section (12.2).9. Conversion of units in FDA laboratory abnormalities table (table 4). |
| 11 November 2011 | Addition of stool samples for microbiome |
| 14 December 2011 | <ol style="list-style-type: none">1. Challenge dose clarified using now available results from study OVG 2009/10, Understanding typhoid disease, Developing a Salmonella Typhi challenge model in healthy adults.2. Section 1.6, Preliminary findings from OVG 2009/10, the OVG challenge study updated.3. Correction to Section 2.1.1.1, 11.2 – post-vaccination symptoms will be recorded for 7 days following the first or only dose has been given.4. Amendment to Section 4.1; individuals over age 60 may be contacted using the electoral role information provided, however are not eligible for study inclusion.5. Clarification of Section 0 and 4.4.1 describing the process of randomisation of participants.6. Addition to 4.4.3 – participants in the functional subgroup will also be asked for additional stool samples for investigation of the faecal microbiome. <p>Correction of blood volume taken taken at typhoid diagnosis calculation in 6.7.3</p> <p>Obtaining participant's height and weight To allow exploratory analysis on the effect of challenge dose per kilo of body weight, participants will be contacted by phone or email to ask them what their height and weight was at the time of challenge. Participants will also be measured and weighed at the CCVTM when attending their next available routine follow up visit if they verbally consent to do so.</p> <ol style="list-style-type: none">7. Table 2: Blood test schedule(5mls more).8. Correction of the e-mail address and fax number for reporting vaccine-related AEs, SAEs and SUSARs to. |
| 15 August 2012 | 2.2 and 7.16 Addition of a participant questionnaire |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Full report of the primary, the secondary end points and the safety reporting are included in the publications.

Secondary end point 7): <https://wellcomeopenresearch.org/articles/4-153/v1>

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/27533046>

<http://www.ncbi.nlm.nih.gov/pubmed/30252031>

<http://www.ncbi.nlm.nih.gov/pubmed/26394303>

<http://www.ncbi.nlm.nih.gov/pubmed/29387052>

<http://www.ncbi.nlm.nih.gov/pubmed/29075261>

<http://www.ncbi.nlm.nih.gov/pubmed/35254093>

<http://www.ncbi.nlm.nih.gov/pubmed/28970824>

<http://www.ncbi.nlm.nih.gov/pubmed/29109704>