



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
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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
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Dictionary used

Dictionary name	Protocol
Dictionary version	5.1

Reporting groups

Reporting group title	Group 1: M01ZH09 vaccine
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Reporting group description:

1 dose, oral; 28 days pre-challenge

Reporting group title	Group 2: placebo
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Reporting group description:

1 dose, oral; 28 days pre-challenge

Reporting group title	Group 3: Ty21a vaccine
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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	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	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. Correction of blood volume taken taken at typhoid diagnosis calculation in 6.7.3 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. 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>