



Clinical trial results:

Preventing meningitis in young people after infant immunisation: effect of a single meningococcal 4CMenB vaccine booster over 10 years of age

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2017-004732-11 |
| Trial protocol | GB |
| Global end of trial date | 28 September 2020 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 24 March 2022 |
| First version publication date | 24 March 2022 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | OVG2017/06 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|----------------|
| ISRCTN number | ISRCTN16774163 |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | University of Oxford, Clinical Trials and Research Governance (CTRG) |
| Sponsor organisation address | Boundary Brook House, Oxford, United Kingdom, OX3 7GB |
| Public contact | Andrew Pollard, University of Oxford, 44 1865611400, andrew.pollard@paediatrics.ox.ac.uk |
| Scientific contact | Andrew 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 | 28 September 2020 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 28 September 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To determine if giving one booster dose of a licensed vaccine (4CMenB) to protect against meningococcal group B disease produces an antibody response that is protective in teenagers who were immunised as infants, as opposed to the two doses that are required for adolescents who have never been vaccinated before.

Protection of trial subjects:

The main side effects of 4CMenB are local reactions, general malaise, and the possibility of fever (although it is more common in infants receiving 4CMenB). This is thoroughly explained in patient information booklets, and we also collect data on these side effects throughout the study to inform future decision-making.

Children who have never received a meningococcal B vaccine before usually require at least 2 doses to become immune to the disease. Adolescent 1 group receive one dose of 4CMenB at the first visit to act as a control for the groups receiving the vaccine once as a booster to their childhood immunisations. However, this single dose would not be enough to provide sufficient level of protection long term. For the participants in Adolescent 1 group not to be disadvantaged when compared with other groups, they are offered a second dose of 4CMenB at day 365. This should provide them with sufficient level of protection as the adolescent vaccine schedule for 4CMenB says that the two required doses should be separated by at least four weeks but does not stipulate an upper limit.

The blood tests that are required to quantify how well the vaccine has induced immunity against meningococcus B can cause some distress to participants. This is mitigated with explanation and reassurance, use of anaesthetic cream or cold spray where necessary, and employment of staff skilled in paediatric venepuncture.

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participants ID number on the source and any electronic CRF. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so. Any data or samples that relate to participants and that leave the study site will be identified by study number and or code only.

Background therapy:

Not applicable

Evidence for comparator:

The 4CMenB vaccine was developed to protect all age groups against group B meningococcal disease. The vaccine was licensed in 2013 in Europe, North America and other jurisdictions, however only the UK has included it in a vaccination programme restricted to infants. The UK schedule consists of three doses administered at 2, 4 and 12 months of age. During clinical development, the vaccine was evaluated in adolescents, and was shown that two doses of 4CMenB induced robust immune responses.

In the UK and in many other countries group B is responsible for the majority of invasive meningococcal disease. Although the number of these cases is currently low in adolescents, 4CMenB could offer protection to those adolescents against this devastating disease, and the vaccine is already licensed for that age group (as a two dose schedule). However, an adolescent program was not initiated in the UK because of the many uncertainties surrounding the vaccine efficacy, duration of protection in this age group and the estimation to not be cost-effective.

In the future, all adolescents in the UK will have received their primary course of 4CMenB vaccination in infancy (currently three doses at 2, 4 +12 months). However no study has yet quantified the immune response in adolescents after a primary course of vaccination with 4CMenB given as babies. The infant 4CMenB vaccination program was only started in 2015 in the UK, and so these children have not yet reached adolescence. While the level of vaccine-induced protective antibody titres against MenB more than 10 years after the last vaccination is expected to be low, previously immunised adolescents may have a substantial level of vaccine-specific memory B-cells. This may in turn produce a strong antibody

recall response to a new encounter with the antigen in the form of a booster vaccine. If this is the case, a single dose adolescent booster could be envisaged as an addition to the current vaccination schedule.

| | |
|---|---------------|
| Actual start date of recruitment | 24 March 2018 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 72 |
| Worldwide total number of subjects | 72 |
| 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) | 49 |
| Adolescents (12-17 years) | 23 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Between 24th March 2018 and 29th January 2019, the trial recruited 72 participants. Forty of the participants were vaccinated with 4CMenB as part of previous studies in 2006-2009 at Oxford.

Pre-assignment

Screening details:

Healthy volunteers (received 4CMenB vaccine as infants as part of clinical trials in 2006 and 2009): 83 invited for screening, 53 responded, 40 enrolled.

Naïve age-matched healthy volunteers: 62 invited for screening, 32 enrolled

Exclusion criteria: previous meningococcal B disease, household contact of bacterial meningitis, immunodeficiency

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Blinding implementation details:

Not applicable

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|------------------|
| Arm title | Follow up cohort |
|------------------|------------------|

Arm description:

Children, born between June and December 2006, who received either an infant 4CMenB schedule (infant group, 2-4-6 + 12 months or 6-8-12 months or just 12 months), or an infant schedule followed by a boost (at 40 months or 40 and 42 months), are given a booster dose of 4CMenB at approximately 11 years of age.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | 4CMenB |
| Investigational medicinal product code | |
| Other name | Bexsero |
| Pharmaceutical forms | Solution for injection in pre-filled syringe |
| Routes of administration | Injection , Intramuscular use |

Dosage and administration details:

supplied in pre-filled 1ml syringes that deliver a single dose of 0.5ml

| | |
|------------------|--------------------|
| Arm title | Adolescent 1 group |
|------------------|--------------------|

Arm description:

Naïve age-matched controls who receive a single dose (day 0) of 4CMenB. For ethical reasons, they are offered a second dose at the end of study (day 365), so they would have received the full adolescent schedule.

| | |
|--|--|
| Arm type | Active comparator |
| Investigational medicinal product name | 4CMenB |
| Investigational medicinal product code | |
| Other name | Bexsero |
| Pharmaceutical forms | Solution for injection in pre-filled syringe |
| Routes of administration | Injection , Intramuscular use |

Dosage and administration details:

supplied in pre-filled 1ml syringes that deliver a single dose of 0.5ml

| | |
|------------------|--------------------|
| Arm title | Adolescent 2 group |
|------------------|--------------------|

Arm description:

Naïve age-matched controls who receive two doses of 4CMenB at day 0 and 28.

| | |
|--|--|
| Arm type | Active comparator |
| Investigational medicinal product name | 4CMenB |
| Investigational medicinal product code | |
| Other name | Bexsero |
| Pharmaceutical forms | Solution for injection in pre-filled syringe |
| Routes of administration | Injection , Intramuscular use |

Dosage and administration details:

supplied in pre-filled 1ml syringes that deliver a single dose of 0.5ml

| Number of subjects in period 1 | Follow up cohort | Adolescent 1 group | Adolescent 2 group |
|---------------------------------------|------------------|--------------------|--------------------|
| Started | 40 | 16 | 16 |
| Completed | 37 | 16 | 14 |
| Not completed | 3 | 0 | 2 |
| Consent withdrawn by subject | 3 | - | 1 |
| failed to obtain blood | - | - | 1 |

Baseline characteristics

Reporting groups

| | |
|---|--------------------|
| Reporting group title | Follow up cohort |
| Reporting group description: Children, born between June and December 2006, who received either an infant 4CMenB schedule (infant group, 2-4-6 + 12 months or 6-8-12 months or just 12 months), or an infant schedule followed by a boost (at 40 months or 40 and 42 months), are given a booster dose of 4CMenB at approximately 11 years of age. | |
| Reporting group title | Adolescent 1 group |
| Reporting group description: Naïve age-matched controls who receive a single dose (day 0) of 4CMenB. For ethical reasons, they are offered a second dose at the end of study (day 365), so they would have received the full adolescent schedule. | |
| Reporting group title | Adolescent 2 group |
| Reporting group description: Naïve age-matched controls who receive two doses of 4CMenB at day 0 and 28. | |

| Reporting group values | Follow up cohort | Adolescent 1 group | Adolescent 2 group |
|---|------------------|--------------------|--------------------|
| Number of subjects | 40 | 16 | 16 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | | |
| Preterm newborn infants (gestational age < 37 wks) | | | |
| Newborns (0-27 days) | | | |
| Infants and toddlers (28 days-23 months) | | | |
| Children (2-11 years) | | | |
| Adolescents (12-17 years) | | | |
| Adults (18-64 years) | | | |
| From 65-84 years | | | |
| 85 years and over | | | |
| Age continuous | | | |
| Age of the participants who received at least one 4CMenB dose. | | | |
| Units: years | | | |
| median | 11.7 | 12.1 | 12.1 |
| inter-quartile range (Q1-Q3) | 11.4 to 12.0 | 11.8 to 12.3 | 11.7 to 12.6 |
| Gender categorical | | | |
| Gender of the participants who received at least one 4CMenB dose. | | | |
| Units: Subjects | | | |
| Female | 23 | 11 | 6 |
| Male | 17 | 5 | 10 |

| Reporting group values | Total | | |
|--|-------|--|--|
| Number of subjects | 72 | | |
| Age categorical | | | |
| 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) | 0 | | |
| From 65-84 years | 0 | | |
| 85 years and over | 0 | | |
| Age continuous | | | |
| Age of the participants who received at least one 4CMenB dose. | | | |
| Units: years | | | |
| median | | | |
| inter-quartile range (Q1-Q3) | - | | |
| Gender categorical | | | |
| Gender of the participants who received at least one 4CMenB dose. | | | |
| Units: Subjects | | | |
| Female | 40 | | |
| Male | 32 | | |

Subject analysis sets

| | |
|--|----------------------------|
| Subject analysis set title | infant group 1 |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| Children who received an infant 4CMenB schedule at 12 months of age (infant group 1), are given a booster dose of 4CMenB at approximately 11 years of age. | |
| Subject analysis set title | infant group 2 |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| Children who received an infant 4CMenB schedule at 6-8-12 months of age (infant group 2), are given a booster dose of 4CMenB at approximately 11 years of age. | |
| Subject analysis set title | infant group 5 |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| Children who received either an infant 4CMenB schedule at 2-4-6 + 12 months of age (infant group 5), are given a booster dose of 4CMenB at approximately 11 years of age. | |
| Subject analysis set title | infant + preschool group 3 |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| Children who received an infant 4CMenB schedule at 12 months of age followed by a boost at 40 and 42 months, are given a booster dose of 4CMenB at approximately 11 years of age. | |
| Subject analysis set title | infant + preschool group 4 |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| Children who received an infant 4CMenB schedule at 6-8-12 months of age followed by a boost at 40 months, are given a booster dose of 4CMenB at approximately 11 years of age. | |
| Subject analysis set title | infant + preschool group 6 |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| Children who received an infant 4CMenB schedule (at 2-4-6 + 12 months of age) followed by a boost at 40 months, are given a booster dose of 4CMenB at approximately 11 years of age. | |
| Subject analysis set title | Adolescent 1 - group 7 |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Naïve age-matched controls who receive a single dose (day 0) of 4CMenB. For ethical reasons, they are offered a second dose at the end of study (day 365), so they would have received the full adolescent schedule.

| | |
|----------------------------|------------------------|
| Subject analysis set title | Adolescent 2 - group 8 |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Naïve age-matched controls who receive two doses of 4CMenB at day 0 and 28.

| Reporting group values | infant group 1 | infant group 2 | infant group 5 |
|---|----------------|----------------|----------------|
| Number of subjects | 4 | 6 | 6 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | | |
| Preterm newborn infants (gestational age < 37 wks) | | | |
| Newborns (0-27 days) | | | |
| Infants and toddlers (28 days-23 months) | | | |
| Children (2-11 years) | | | |
| Adolescents (12-17 years) | | | |
| Adults (18-64 years) | | | |
| From 65-84 years | | | |
| 85 years and over | | | |
| Age continuous | | | |
| Age of the participants who received at least one 4CMenB dose. | | | |
| Units: years | | | |
| median | 11.6 | 11.8 | 11.5 |
| inter-quartile range (Q1-Q3) | 11.4 to 11.8 | 11.4 to 12.0 | 11.5 to 11.8 |
| Gender categorical | | | |
| Gender of the participants who received at least one 4CMenB dose. | | | |
| Units: Subjects | | | |
| Female | 1 | 3 | 4 |
| Male | 3 | 3 | 2 |

| Reporting group values | infant + preschool group 3 | infant + preschool group 4 | infant + preschool group 6 |
|--|----------------------------|----------------------------|----------------------------|
| Number of subjects | 4 | 9 | 11 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | | |
| Preterm newborn infants (gestational age < 37 wks) | | | |
| Newborns (0-27 days) | | | |
| Infants and toddlers (28 days-23 months) | | | |
| Children (2-11 years) | | | |
| Adolescents (12-17 years) | | | |
| Adults (18-64 years) | | | |
| From 65-84 years | | | |
| 85 years and over | | | |
| Age continuous | | | |
| Age of the participants who received at least one 4CMenB dose. | | | |
| Units: years | | | |

| | | | |
|------------------------------|--------------|--------------|--------------|
| median | 11.6 | 11.7 | 11.6 |
| inter-quartile range (Q1-Q3) | 11.4 to 11.7 | 11.4 to 12.0 | 11.4 to 11.9 |

| | | | |
|---|---|---|---|
| Gender categorical | | | |
| Gender of the participants who received at least one 4CMenB dose. | | | |
| Units: Subjects | | | |
| Female | 2 | 7 | 6 |
| Male | 2 | 2 | 5 |

| | | | |
|---|---------------------------|---------------------------|--|
| Reporting group values | Adolescent 1 - group 7 | Adolescent 2 - group 8 | |
| Number of subjects | 16 | 16 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | | |
| Preterm newborn infants (gestational age < 37 wks) | | | |
| Newborns (0-27 days) | | | |
| Infants and toddlers (28 days-23 months) | | | |
| Children (2-11 years) | | | |
| Adolescents (12-17 years) | | | |
| Adults (18-64 years) | | | |
| From 65-84 years | | | |
| 85 years and over | | | |
| Age continuous | | | |
| Age of the participants who received at least one 4CMenB dose. | | | |
| Units: years | | | |
| median | 12.1 | 12.1 | |
| inter-quartile range (Q1-Q3) | 11.8 to 12.3 | 11.7 to 12.6 | |
| Gender categorical | | | |
| Gender of the participants who received at least one 4CMenB dose. | | | |
| Units: Subjects | | | |
| Female | 11 | 6 | |
| Male | 5 | 10 | |

End points

End points reporting groups

| | |
|---|----------------------------|
| Reporting group title | Follow up cohort |
| Reporting group description: Children, born between June and December 2006, who received either an infant 4CMenB schedule (infant group, 2-4-6 + 12 months or 6-8-12 months or just 12 months), or an infant schedule followed by a boost (at 40 months or 40 and 42 months), are given a booster dose of 4CMenB at approximately 11 years of age. | |
| Reporting group title | Adolescent 1 group |
| Reporting group description: Naïve age-matched controls who receive a single dose (day 0) of 4CMenB. For ethical reasons, they are offered a second dose at the end of study (day 365), so they would have received the full adolescent schedule. | |
| Reporting group title | Adolescent 2 group |
| Reporting group description: Naïve age-matched controls who receive two doses of 4CMenB at day 0 and 28. | |
| Subject analysis set title | infant group 1 |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Children who received an infant 4CMenB schedule at 12 months of age (infant group 1), are given a booster dose of 4CMenB at approximately 11 years of age. | |
| Subject analysis set title | infant group 2 |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Children who received an infant 4CMenB schedule at 6-8-12 months of age (infant group 2), are given a booster dose of 4CMenB at approximately 11 years of age. | |
| Subject analysis set title | infant group 5 |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Children who received either an infant 4CMenB schedule at 2-4-6 + 12 months of age (infant group 5), are given a booster dose of 4CMenB at approximately 11 years of age. | |
| Subject analysis set title | infant + preschool group 3 |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Children who received an infant 4CMenB schedule at 12 months of age followed by a boost at 40 and 42 months, are given a booster dose of 4CMenB at approximately 11 years of age. | |
| Subject analysis set title | infant + preschool group 4 |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Children who received an infant 4CMenB schedule at 6-8-12 months of age followed by a boost at 40 months, are given a booster dose of 4CMenB at approximately 11 years of age. | |
| Subject analysis set title | infant + preschool group 6 |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Children who received an infant 4CMenB schedule (at 2-4-6 + 12 months of age) followed by a boost at 40 months, are given a booster dose of 4CMenB at approximately 11 years of age. | |
| Subject analysis set title | Adolescent 1 - group 7 |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Naïve age-matched controls who receive a single dose (day 0) of 4CMenB. For ethical reasons, they are offered a second dose at the end of study (day 365), so they would have received the full adolescent schedule. | |
| Subject analysis set title | Adolescent 2 - group 8 |

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

Naïve age-matched controls who receive two doses of 4CMenB at day 0 and 28.

Primary: Fold change in hSBA titre between Day 0 and Day 180

| | |
|-----------------|--|
| End point title | Fold change in hSBA titre between Day 0 and Day 180 ^[1] |
|-----------------|--|

End point description:

Calculation of the median of fold change in hSBA titre Day 180 value to Day 0 value.

Results are reported as median of fold change with IQR, instead of geometric mean with 95% CI due to the small numbers.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Fold change from Day 0 to Day 180

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This is a descriptive study and does not involve hypothesis testing for p-value.

| End point values | infant group 1 | infant group 2 | infant group 5 | infant + preschool group 3 |
|---------------------------------------|----------------------|----------------------|----------------------|----------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 4 | 5 | 6 | 4 |
| Units: Fold change in hSBA | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| strain 5/99 | 72 (12 to 160) | 8 (4 to 128) | 24 (5 to 104) | 20 (6 to 56) |
| strain NZ98/254 | 1 (1 to 1) | 8 (1 to 8) | 2 (1 to 2) | 2 (2 to 2) |
| strain 44/76-SL | 2 (1 to 5) | 1 (1 to 16) | 1 (1 to 1) | 4 (1 to 14) |

| End point values | infant + preschool group 4 | infant + preschool group 6 | Adolescent 1 - group 7 | Adolescent 2 - group 8 |
|---------------------------------------|----------------------------|----------------------------|------------------------|------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 9 | 10 | 15 | 15 |
| Units: Fold change in hSBA | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| strain 5/99 | 32 (16 to 64) | 16 (4 to 112) | 2 (2 to 4) | 64 (64 to 128) |
| strain NZ98/254 | 4 (2 to 16) | 4 (2 to 4) | 1 (1 to 6) | 4 (2 to 12) |
| strain 44/76-SL | 8 (4 to 32) | 4 (2 to 16) | 1 (1 to 1) | 4 (1 to 8) |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

For the first 7 days after immunisation at visit 1 (all study groups), visit 2 (group 8 only) and visit 4 (group 7 only) all AEs observed by the study team or reported by the participant's parent/legal guardian, are recorded in the eDiary.

Adverse event reporting additional description:

Description, onset and end date, severity, assessment of relatedness to study vaccine and action taken are recorded. Any medication taken to treat an AE is recorded. Reactions occurring in the first 7 days after immunisation are divided into solicited and unsolicited.

Non-serious AE are not part of the study objectives and are not reported here.

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

Dictionary used

| | |
|--------------------|----------|
| Dictionary name | Protocol |
| Dictionary version | v4.0 |

Reporting groups

| | |
|-----------------------|------------------|
| Reporting group title | Follow up cohort |
|-----------------------|------------------|

Reporting group description:

Children, born between June and December 2006, who received either an infant 4CMenB schedule (infant group, 2-4-6 + 12 months or 6-8-12 months or just 12 months), or an infant schedule followed by a boost (at 40 months or 40 and 42 months), are given a booster dose of 4CMenB at approximately 11 years of age.

Follow up cohort consists of protocol groups 1-6.

| | |
|-----------------------|--------------------|
| Reporting group title | Adolescent 1 group |
|-----------------------|--------------------|

Reporting group description:

Naïve age-matched controls who receive a single dose (day 0) of 4CMenB. For ethical reasons, they are offered a second dose at the end of study (day 365), so they would have received the full adolescent schedule.

| | |
|-----------------------|--------------------|
| Reporting group title | Adolescent 2 group |
|-----------------------|--------------------|

Reporting group description:

Naïve age-matched controls who receive two doses of 4CMenB at day 0 and 28.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: Non-serious adverse events are not part of the study objectives and are not reported here. Full details of non-serious adverse events will be provided in the study publication.

| Serious adverse events | Follow up cohort | Adolescent 1 group | Adolescent 2 group |
|---|--|--------------------|--------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 40 (5.00%) | 2 / 16 (12.50%) | 1 / 16 (6.25%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Surgical and medical procedures | | | |
| Phimosis | Additional description: Mild, not related to study vaccine, pre-existing condition | | |
| subjects affected / exposed | 0 / 40 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (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 |
| Gastrointestinal disorders | | | |
| Acute appendicitis | Additional description: Moderate, not related to study vaccine | | |

| | | | |
|---|--|----------------|----------------|
| subjects affected / exposed | 1 / 40 (2.50%) | 0 / 16 (0.00%) | 0 / 16 (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 |
| Appendicitis | Additional description: Moderate, not related to study vaccine | | |
| subjects affected / exposed | 0 / 40 (0.00%) | 0 / 16 (0.00%) | 1 / 16 (6.25%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Unexplained lower limb weakness | Additional description: Severe, not related to study vaccine | | |
| subjects affected / exposed | 1 / 40 (2.50%) | 0 / 16 (0.00%) | 0 / 16 (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 |
| Broken left wrist and green stick fracture | Additional description: Moderate, not related to study vaccine | | |
| subjects affected / exposed | 0 / 40 (0.00%) | 1 / 16 (6.25%) | 0 / 16 (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 | Follow up cohort | Adolescent 1 group | Adolescent 2 group |
|---|------------------|--------------------|--------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | 0 / 16 (0.00%) | 0 / 16 (0.00%) |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|--|
| 30 January 2018 | .Addition of an option to return a reply slip for previously vaccinated participants when indicating whether they would like to take part in this study. .Changing the randomisation of patients in the naïve group from a computer-based system (Sortition) to a paper envelope based system to avoid issues with internet access on site. |
| 19 March 2018 | .Amended the protocol and parent and assenting information booklets to change the use of the continuous temperature monitoring device to being optional. .Added reply slips for GP and CHIS letters so they can let us know if they have managed to forward the invitation pack on to the family. Amended typographical errors in group card 7&8, Study labels and the assenting information booklet for non-naïves. |
| 21 June 2018 | .Changing of the statistical analysis section to include a descriptive analysis of immunogenicity at 180 days, and changes to the wording of the how the analysis will be done. .Changing the wording of the exclusion criteria (changed "bacterial" meningitis to "meningococcal" meningitis). .Updating the PIL to change the details of where to opt-out of receiving study mail and to update GDPR details. |

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.

Publication of results is in draft and will be published soon and distributed to participants. It will include the secondary objectives and non-serious adverse events, which are not reported here.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/31340842>