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 does 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 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 7days 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 recorder. 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-serous 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-serous 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-naives.
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