



Clinical trial results:

INVESTIGATING THE CLINICAL USE OF 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE (PREVENAR) IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKAEMIA

Summary

EudraCT number	2009-011587-11
Trial protocol	GB
Global end of trial date	20 November 2015

Results information

Result version number	v1 (current)
This version publication date	15 February 2017
First version publication date	15 February 2017

Trial information

Trial identification

Sponsor protocol code	RHMCAN0658
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Additional study identifiers

ISRCTN number	ISRCTN12861513
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Short name: PCV13inALL

Notes:

Sponsors

Sponsor organisation name	University Hospital Southampton NHS Foundation Trust
Sponsor organisation address	Southampton General Hospital , Southampton, United Kingdom, SO16 6YD
Public contact	Elizabeth Dixon, Trials Mana, University of Southampton CTU, 0044 2381205154, e.dixon@soton.ac.uk
Scientific contact	Elizabeth Dixon, Trials Mana, University of Southampton CTU, 0044 2381205154, e.dixon@soton.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	16 November 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 August 2015
Global end of trial reached?	Yes
Global end of trial date	20 November 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The principal research question is whether immunisation with a pneumococcal vaccine (13vPCV) can be used to protect children with Acute Lymphoblastic Leukaemia from pneumococcal infection. It will seek to identify the earliest time-point in treatment that children can be effectively vaccinated in order to protect children from this infection for as long as possible, when they are most at risk of infection. Specifically, it will investigate whether protective pneumococcal immunity can be achieved by immunising with 13vPCV:

- a) during leukaemia treatment (during maintenance chemotherapy)?
- b) at the end of leukaemia treatment?
- c) 6 months after completion of leukaemia treatment?

Protection of trial subjects:

None

Background therapy:

None

Evidence for comparator:

None

Actual start date of recruitment	01 September 2010
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: 118
Worldwide total number of subjects	118
EEA total number of subjects	118

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)	91
Adolescents (12-17 years)	27
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

118 patients were recruited from Sept 2010 to July 2015 from 8 hospital sites in the UK. Children were allocated to study groups empirically, on the basis of their current time point in ALL treatment: Either during maintenance chemotherapy and 6 months from intensive chemotherapy; at the end of treatment or 6 months after completion of treatment.

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	224 ^[1]
Number of subjects completed	118

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Clinician choice: 6
Reason: Number of subjects	Not fit at time and did not reschedule: 12
Reason: Number of subjects	Patient choice - bloods: 10
Reason: Number of subjects	Patient choice - distance: 16
Reason: Number of subjects	Patient choice - other: 32
Reason: Number of subjects	Patient choice - vaccine: 3
Reason: Number of subjects	Research team did not approach in time frame: 14
Reason: Number of subjects	Not eligible: 13

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 224 subjects were actively screened and for the reasons presented in the table below, 106 did not complete the pre-assignment period.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Study Group 1

Arm description:

6 months from end of last intensification

The exact timing of vaccination will depend on which UKALL 2003 chemotherapy regime the child is receiving (A, B or C), and should also be timed to avoid concomitant administration of oral dexamethasone. Ideally children should be vaccinated when they attend for lumbar puncture and intrathecal methotrexate during maintenance cycle 3. If vaccination at this time point is not possible then it may be performed 4 weeks later, at least 7 days after completion of dexamethasone and no less than 7 days before the next pulse of dexamethasone is due. If vaccination at this point is not possible then the patient should be re-allocated to study group 2 or 3.

Arm type	Timing of vaccination
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Investigational medicinal product name	Prevenar-13
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

PCV13 (Prevenar-13TM) will be supplied by Wyeth as pre-filled syringes containing 0.5 ml of homogenous white suspension. Vaccine must be stored in a pharmacy refrigerator (2–8oC) until administration. A single 0.5 ml dose of vaccine should be administered to each study patient as specified in section 3.5. The vaccine should be given intramuscularly in either the anterolateral aspect of the deltoid. The needle to be used is a blue, gauge: 23g x 25mm.

Arm title	Study Group 2
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Arm description:

On completion of maintenance chemotherapy

Vaccination should be given 4 weeks after the last dose of oral chemotherapy. If vaccination is not possible at this time point it may be delayed for up to 4 weeks. If vaccination has not taken place by this point the patient should be re-allocated to study group 3

Arm type	Timing of vaccination
Investigational medicinal product name	Prevenar-13
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

PCV13 (Prevenar-13TM) will be supplied by Wyeth as pre-filled syringes containing 0.5 ml of homogenous white suspension. Vaccine must be stored in a pharmacy refrigerator (2–8oC) until administration. A single 0.5 ml dose of vaccine should be administered to each study patient as specified in section 3.5. The vaccine should be given intramuscularly in either the anterolateral aspect of the deltoid. The needle to be used is a blue, gauge: 23g x 25mm.

Arm title	Study Group 3
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Arm description:

6 months after completion of chemotherapy

Vaccination should be given 6 months after the last dose of oral chemotherapy. If vaccination is not possible at this time point it may be delayed for up to 4 weeks. If vaccination has not taken place by this point the patient is no longer eligible for the study.

Arm type	Timing of vaccination
Investigational medicinal product name	Prevenar-13
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

PCV13 (Prevenar-13TM) will be supplied by Wyeth as pre-filled syringes containing 0.5 ml of homogenous white suspension. Vaccine must be stored in a pharmacy refrigerator (2–8oC) until administration. A single 0.5 ml dose of vaccine should be administered to each study patient as specified in section 3.5. The vaccine should be given intramuscularly in either the anterolateral aspect of the deltoid. The needle to be used is a blue, gauge: 23g x 25mm.

Number of subjects in period 1	Study Group 1	Study Group 2	Study Group 3
Started	39	40	39
Completed	37	32	34
Not completed	2	8	5
Consent withdrawn by subject	1	2	2
Receiving pallative care	-	1	-
Death	1	-	-
Re-vaccination against PCV	-	1	-
Transferred to another hospital	-	-	1
Lost to follow-up	-	3	2
Protocol deviation	-	1	-

Baseline characteristics

Reporting groups

Reporting group title	Study Group 1
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Reporting group description:

6 months from end of last intensification

The exact timing of vaccination will depend on which UKALL 2003 chemotherapy regime the child is receiving (A, B or C), and should also be timed to avoid concomitant administration of oral dexamethasone. Ideally children should be vaccinated when they attend for lumbar puncture and intrathecal methotrexate during maintenance cycle 3. If vaccination at this time point is not possible then it may be performed 4 weeks later, at least 7 days after completion of dexamethasone and no less than 7 days before the next pulse of dexamethasone is due. If vaccination at this point is not possible then the patient should be re-allocated to study group 2 or 3.

Reporting group title	Study Group 2
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Reporting group description:

On completion of maintenance chemotherapy

Vaccination should be given 4 weeks after the last dose of oral chemotherapy. If vaccination is not possible at this time point it may be delayed for up to 4 weeks. If vaccination has not taken place by this point the patient should be re-allocated to study group 3

Reporting group title	Study Group 3
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Reporting group description:

6 months after completion of chemotherapy

Vaccination should be given 6 months after the last dose of oral chemotherapy. If vaccination is not possible at this time point it may be delayed for up to 4 weeks. If vaccination has not taken place by this point the patient is no longer eligible for the study.

Reporting group values	Study Group 1	Study Group 2	Study Group 3
Number of subjects	39	40	39
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 Units: years			
arithmetic mean	6.3	8.4	9.3
full range (min-max)	2 to 17	4 to 17	4 to 17
Gender categorical Units: Subjects			
Female	16	17	14
Male	23	23	25

Treatment Protocol			
Units: Subjects			
UKALL 2003 Regimen A	22	25	21
UKALL 2003 Regimen B	7	10	11
UKALL 2003 Regimen C	10	5	7
Number of delayed intensifications			
Units: Subjects			
One	15	19	16
Two	24	21	23

Reporting group values	Total		
Number of subjects	118		
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			
Units: years			
arithmetic mean			
full range (min-max)	-		
Gender categorical			
Units: Subjects			
Female	47		
Male	71		
Treatment Protocol			
Units: Subjects			
UKALL 2003 Regimen A	68		
UKALL 2003 Regimen B	28		
UKALL 2003 Regimen C	22		
Number of delayed intensifications			
Units: Subjects			
One	50		
Two	68		

Subject analysis sets

Subject analysis set title	Analysis population
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All patients who have received a PCV-13 vaccination during the study will be included in the analysis population for the immunogenicity and safety analyses.

Reporting group values	Analysis population		
Number of subjects	117		
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 Units: years			
arithmetic mean	8		
full range (min-max)	2 to 17		
Gender categorical Units: Subjects			
Female	47		
Male	70		
Treatment Protocol Units: Subjects			
UKALL 2003 Regimen A	67		
UKALL 2003 Regimen B	28		
UKALL 2003 Regimen C	22		
Number of delayed intensifications Units: Subjects			
One	49		
Two	68		

End points

End points reporting groups

Reporting group title	Study Group 1
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Reporting group description:

6 months from end of last intensification

The exact timing of vaccination will depend on which UKALL 2003 chemotherapy regime the child is receiving (A, B or C), and should also be timed to avoid concomitant administration of oral dexamethasone. Ideally children should be vaccinated when they attend for lumbar puncture and intrathecal methotrexate during maintenance cycle 3. If vaccination at this time point is not possible then it may be performed 4 weeks later, at least 7 days after completion of dexamethasone and no less than 7 days before the next pulse of dexamethasone is due. If vaccination at this point is not possible then the patient should be re-allocated to study group 2 or 3.

Reporting group title	Study Group 2
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Reporting group description:

On completion of maintenance chemotherapy

Vaccination should be given 4 weeks after the last dose of oral chemotherapy. If vaccination is not possible at this time point it may be delayed for up to 4 weeks. If vaccination has not taken place by this point the patient should be re-allocated to study group 3

Reporting group title	Study Group 3
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Reporting group description:

6 months after completion of chemotherapy

Vaccination should be given 6 months after the last dose of oral chemotherapy. If vaccination is not possible at this time point it may be delayed for up to 4 weeks. If vaccination has not taken place by this point the patient is no longer eligible for the study.

Subject analysis set title	Analysis population
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

All patients who have received a PCV-13 vaccination during the study will be included in the analysis population for the immunogenicity and safety analyses.

Primary: Response in concentration of serotype specific anti-pneumococcal antibodies at 1 month post-vaccination

End point title	Response in concentration of serotype specific anti-pneumococcal antibodies at 1 month post-vaccination ^[1]
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End point description:

A patient is classified as a responder if their results at 1 month for at least 10 out of the 12 serotypes (or greater than 83% of serotypes with data) satisfy the following condition, which is defined by the World Health Organisation (WHO):

1 month post-vaccination serotype-specific IgG ≥ 0.35 $\mu\text{g/ml}$ and ≥ 4 fold rise compared to pre-vaccination.

End point type	Primary
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End point timeframe:

1 month post-vaccination compared to baseline

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: The primary end point did not compare the study groups. The results of the analysis of the primary end point are presented in another table which provides the proportion of responders per group and their corresponding 95% confidence intervals

End point values	Study Group 1	Study Group 2	Study Group 3	Analysis population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	39	37	37	113
Units: Proportion				
number (confidence interval 95%)	12.8 (4.3 to 27.4)	59.5 (42.1 to 75.3)	56.8 (39.5 to 72.9)	42.5 (33.2 to 52.1)

Statistical analyses

No statistical analyses for this end point

Primary: Response in concentration of serotype specific anti-pneumococcal antibodies at 12 months post-vaccination

End point title	Response in concentration of serotype specific anti-pneumococcal antibodies at 12 months post-vaccination ^[2]
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End point description:

A patient is classified as a responder if their results at 12 months for at least 10 out of the 12 serotypes (or greater than 83% of serotypes with data) satisfy the following condition, which is defined by the WHO:

12 months post-vaccination serotype-specific IgG \geq 0.35 μ g/ml and \geq 4 fold rise compared to pre-vaccination.

End point type	Primary
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End point timeframe:

12 months post-vaccination compared to baseline

Notes:

[2] - 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: The primary end point did not compare the study groups. The results of the analysis of the primary end point are presented in another table which provides the proportion of responders per group and their corresponding 95% confidence intervals

End point values	Study Group 1	Study Group 2	Study Group 3	Analysis population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	37	29	30	96
Units: Proportion				
number (confidence interval 95%)	0 (0 to 0)	37.9 (20.7 to 57.7)	43.3 (25.5 to 62.6)	25 (16.7 to 34.9)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall composite response in anti-pneumococcal antibodies at 1 month post-vaccination

End point title	Overall composite response in anti-pneumococcal antibodies at 1 month post-vaccination
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End point description:

A patient is classified as a responder if they are a responder in both the following endpoints:

a) A patient is classified as a responder if their results at 1 month for at least 10 out of the 12 serotypes (or greater than 83% of serotypes with data) satisfy the following condition, which is defined by the World Health Organisation (WHO): 1 month post-vaccination serotype-specific IgG $\geq 0.35 \mu\text{g/ml}$ and ≥ 4 fold rise compared to pre-vaccination.

b) A patient is classified as a responder if their results at 1 month for all 4 serotypes satisfy the following condition:

Opsonophagocytosis assay (OPA) titre $\geq 1:8$ dilution at 1 month post-vaccination.

(i.e. have a response in concentration of anti-pneumococcal antibodies and a response in functionality of anti-pneumococcal antibodies at 1 month).

End point type	Secondary
End point timeframe:	
1 month post-vaccination compared to baseline	

End point values	Study Group 1	Study Group 2	Study Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39	36	34	
Units: Number	4	17	17	

Statistical analyses

Statistical analysis title	Logistic regression - Study group: 1 vs 2
Comparison groups	Study Group 1 v Study Group 2
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	0.46

Statistical analysis title	Logistic regression - Study group: 1 vs 3
Comparison groups	Study Group 1 v Study Group 3

Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.03
upper limit	0.4

Statistical analysis title	Logistic regression - Study group: 2 vs 3
Comparison groups	Study Group 3 v Study Group 2
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.725
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.32
upper limit	2.2

Secondary: Overall composite response in anti-pneumococcal antibodies at 12 months post-vaccination

End point title	Overall composite response in anti-pneumococcal antibodies at 12 months post-vaccination
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End point description:

A patient is classified as a responder if they are a responder in both the following endpoints:

a) A patient is classified as a responder if their results at 12 months for at least 10 out of the 12 serotypes (or greater than 83% of serotypes with data) satisfy the following condition, which is defined by the WHO: 12 months post-vaccination serotype-specific IgG ≥ 0.35 $\mu\text{g/ml}$ and ≥ 4 fold rise compared to pre-vaccination.

b) A patient is classified as a responder if their results at 12 months for all 4 serotypes satisfy the following condition: Opsonophagocytosis assay (OPA) titre $\geq 1:8$ dilution at 12 months post-vaccination.

(i.e. have a response in concentration of anti-pneumococcal antibodies and a response in functionality of anti-pneumococcal antibodies at 12 months).

End point type	Secondary
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End point timeframe:

12 months post-vaccination compared to baseline

End point values	Study Group 1	Study Group 2	Study Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	27	30	
Units: Number	0	5	8	

Statistical analyses

Statistical analysis title	Logistic regression - Study groups: 2 vs 3
Comparison groups	Study Group 2 v Study Group 3
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.406
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.16
upper limit	2.11

Secondary: Temperature seven days after vaccination

End point title	Temperature seven days after vaccination
End point description:	
Maximum temperature reported during the seven days post-vaccination	
End point type	Secondary
End point timeframe:	
During seven days post-vaccination	

End point values	Study Group 1	Study Group 2	Study Group 3	Analysis population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	35	38	36	109
Units: Number				
< 38 *C	32	37	29	98
Fever >= 38 *C but <= 40 *C	5	1	7	11
Fever > 40 *C	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Redness at the site of the injection for each of the seven days after vaccination

End point title	Redness at the site of the injection for each of the seven days after vaccination
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End point description:

Maximum redness experienced during seven days post-vaccination

End point type	Secondary
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End point timeframe:

Seven days post-vaccination

End point values	Study Group 1	Study Group 2	Study Group 3	Analysis population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	26	29	26	81
Units: Number				
No redness	12	8	13	33
> 0 to < 1 cm	5	11	8	24
>= 1 cm to < 2.5 cm	0	5	1	6
>= 2.5 cm to < 5 cm	3	1	2	6
>= 5 cm	6	4	2	12

Statistical analyses

No statistical analyses for this end point

Secondary: Swelling at the site of the injection for each of the seven days after vaccination

End point title	Swelling at the site of the injection for each of the seven days after vaccination
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End point description:

Maximum swelling during seven days post-vaccination

End point type	Secondary
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End point timeframe:

Seven days post-vaccination

End point values	Study Group 1	Study Group 2	Study Group 3	Analysis population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	22	27	22	71
Units: Number				
No swelling	12	18	15	45
> 0 to < 1 cm	4	2	4	10
>= 1 cm to < 2.5 cm	2	3	1	6
>= 2.5 cm to < 5 cm	2	2	1	5
>= 5 cm	2	2	1	5

Statistical analyses

No statistical analyses for this end point

Secondary: Pain at the site of the injection for each of the seven days after vaccination

End point title	Pain at the site of the injection for each of the seven days after vaccination
End point description:	
Maximum pain experienced during seven days post-vaccination	
End point type	Secondary
End point timeframe:	
Seven days post-vaccination	

End point values	Study Group 1	Study Group 2	Study Group 3	Analysis population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	36	37	35	108
Units: Number				
None	10	4	3	17
Mild	16	18	13	47
Moderate	7	12	14	33
Severe	3	3	5	11

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs are collected for 12 months post vaccination.

Adverse event reporting additional description:

At each contact with the patient, the investigator sought information on adverse events by specific questioning and, as appropriate, by examination. The clinical course of each event should be followed until resolution, stabilisation, or until it has been determined that the study treatment or participation is not the cause.

Assessment type	Systematic
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Dictionary used

Dictionary name	CTCAE
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Dictionary version	4
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Reporting groups

Reporting group title	Study Group 1
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Reporting group description:

6 months from end of last intensification

The exact timing of vaccination will depend on which UKALL 2003 chemotherapy regime the child is receiving (A, B or C), and should also be timed to avoid concomitant administration of oral dexamethasone. Ideally children should be vaccinated when they attend for lumbar puncture and intrathecal methotrexate during maintenance cycle 3. If vaccination at this time point is not possible then it may be performed 4 weeks later, at least 7 days after completion of dexamethasone and no less than 7 days before the next pulse of dexamethasone is due. If vaccination at this point is not possible then the patient should be re-allocated to study group 2 or 3.

Reporting group title	Study Group 2
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Reporting group description:

On completion of maintenance chemotherapy

Vaccination should be given 4 weeks after the last dose of oral chemotherapy. If vaccination is not possible at this time point it may be delayed for up to 4 weeks. If vaccination has not taken place by this point the patient should be re-allocated to study group 3

Reporting group title	Study Group 3
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Reporting group description:

6 months after completion of chemotherapy

Vaccination should be given 6 months after the last dose of oral chemotherapy. If vaccination is not possible at this time point it may be delayed for up to 4 weeks. If vaccination has not taken place by this point the patient is no longer eligible for the study.

Serious adverse events	Study Group 1	Study Group 2	Study Group 3
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 39 (17.95%)	3 / 40 (7.50%)	1 / 39 (2.56%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	0	0	0
General disorders and administration site conditions			
Fever			

subjects affected / exposed	2 / 39 (5.13%)	1 / 40 (2.50%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Flu like symptoms			
subjects affected / exposed	1 / 39 (2.56%)	0 / 40 (0.00%)	0 / 39 (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
Infections and infestations			
Lung infection			
subjects affected / exposed	1 / 39 (2.56%)	0 / 40 (0.00%)	0 / 39 (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
Other			
subjects affected / exposed	2 / 39 (5.13%)	2 / 40 (5.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	1 / 39 (2.56%)	0 / 40 (0.00%)	0 / 39 (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

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Study Group 1	Study Group 2	Study Group 3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 39 (87.18%)	29 / 40 (72.50%)	21 / 39 (53.85%)
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications - Other			
subjects affected / exposed	0 / 39 (0.00%)	2 / 40 (5.00%)	0 / 39 (0.00%)
occurrences (all)	0	2	0
Surgical and medical procedures			
Surgical and medical procedures - Other			

subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2	0 / 40 (0.00%) 0	0 / 39 (0.00%) 0
Nervous system disorders Headache subjects affected / exposed occurrences (all)	3 / 39 (7.69%) 4	2 / 40 (5.00%) 2	2 / 39 (5.13%) 2
Blood and lymphatic system disorders Febrile Neutropenia subjects affected / exposed occurrences (all)	12 / 39 (30.77%) 18	0 / 40 (0.00%) 0	0 / 39 (0.00%) 0
General disorders and administration site conditions Fever/Flu like symptoms subjects affected / exposed occurrences (all) General disorders and administration site conditions - Other subjects affected / exposed occurrences (all)	17 / 39 (43.59%) 28 3 / 39 (7.69%) 4	5 / 40 (12.50%) 6 1 / 40 (2.50%) 1	6 / 39 (15.38%) 6 0 / 39 (0.00%) 0
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Diarrhoea and vomiting subjects affected / exposed occurrences (all)	3 / 39 (7.69%) 3 3 / 39 (7.69%) 4	2 / 40 (5.00%) 2 1 / 40 (2.50%) 1	1 / 39 (2.56%) 1 0 / 39 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Respiratory, thoracic and mediastinal disorders - Other subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	2 / 40 (5.00%) 2	1 / 39 (2.56%) 1
Skin and subcutaneous tissue disorders Rash/skin disorder subjects affected / exposed occurrences (all)	7 / 39 (17.95%) 8	2 / 40 (5.00%) 2	2 / 39 (5.13%) 2
Musculoskeletal and connective tissue disorders Fracture/Musculoskeletal			

subjects affected / exposed occurrences (all)	4 / 39 (10.26%) 4	4 / 40 (10.00%) 6	2 / 39 (5.13%) 3
Infections and infestations			
Central line infection			
subjects affected / exposed	6 / 39 (15.38%)	0 / 40 (0.00%)	0 / 39 (0.00%)
occurrences (all)	10	0	0
Cough/Lower respiratory tract infection			
subjects affected / exposed	10 / 39 (25.64%)	6 / 40 (15.00%)	2 / 39 (5.13%)
occurrences (all)	17	7	3
Infection-other			
subjects affected / exposed	6 / 39 (15.38%)	2 / 40 (5.00%)	0 / 39 (0.00%)
occurrences (all)	8	2	0
Upper respiratory tract infection			
subjects affected / exposed	15 / 39 (38.46%)	7 / 40 (17.50%)	10 / 39 (25.64%)
occurrences (all)	24	9	13
Viral illness			
subjects affected / exposed	8 / 39 (20.51%)	4 / 40 (10.00%)	2 / 39 (5.13%)
occurrences (all)	10	4	2
Viral infection			
subjects affected / exposed	5 / 39 (12.82%)	4 / 40 (10.00%)	2 / 39 (5.13%)
occurrences (all)	8	4	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 June 2010	<p>1. Reduction in number of investigations Two rather than three nasopharyngeal swabs per subject over study period. Change made as it was felt that little extra information would be gained from a third swab.</p> <p>2. Change in reporting of SAE's SAEs only require report up to 28 days after vaccine administration as prolonged follow up is require to monitor for vaccine efficacy rather than safety. A significant number of SAR are likely to occur during the 123 month study period because of the underlying disease and treatment (on-study medications) that the study population are receiving. With the exception of events happening in the first few days after PCV vaccination, it is extremely unlikely that AEs would have been related to IMP or any study procedures. All would be captured but only those in the first 28 days following IMP administration will be formally reported as a SAE.</p>
03 January 2012	Inclusion of more detailed statistical analysis plan, with clarification of endpoints
04 April 2012	<p>Addition of the following secondary end points for clarity:</p> <ul style="list-style-type: none">i) to establish if any of the serotypes are more effective or less effective at inducing protective levels of anti-pneumococcal antibodies in the studyii) to assess whether leukaemia treatment regimen or number of delayed intensifications are associated with (or affect response to) developing protective levels of anti-pneumococcal antibodiesiii) to establish whether PCV13 is more or less effective in any of study groups in terms of inducing protective levels of anti-pneumococcal antibodiesiv) to investigate the immunogenicity of the vaccine in children who have already had the PCV7 (serotypes 4, 6B, 9V, 14, 18C, 19F and 23F) prior to entering the study <p>Amendment to inclusion criteria- wording in brackets added 'Currently receiving maintenance therapy as per (current UKALL interim guidelines or) UKALL 2003 treatment protocol, or treatment as per UKALL 2003 protocol'</p> <p>Amendment to exclusion criteria Addition of 'Previous immunisation with PCV13 prior to the study'</p>

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.

None

Notes: