Clinical trial results:
Single arm NCRI feasibility study of CHOP in combination with Ofatumumab in induction and maintenance for patients with newly diagnosed Richter's Syndrome

Summary

EudraCT number	2009-016459-23
Trial protocol	GB
Global end of trial date	19 April 2016

Results information

Result version number	v2 (current)
This version publication date	15 July 2017
First version publication date	10 May 2017
Version creation reason	• Correction of full data set Correction of full data set

Trial information

Trial identification

Sponsor protocol code	OCTO_018

Additional study identifiers

ISRCTN number	ISRCTN88860946
ClinicalTrials.gov id (NCT number)	NCT01171378
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Oxford
Sponsor organisation address	Joint Research Office, Block 60, Churchill Hospital, Old Road, Oxford, United Kingdom, OX3 7LE
Public contact	Heather House, University of Oxford, +44 1865 572245, ctrg@admin.ox.ac.uk
Scientific contact	Heather House, University of Oxford, +44 1865 572245, ctrg@admin.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	02 February 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 February 2015
Global end of trial reached?	Yes
Global end of trial date	19 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to determine objective response to ofatumumab plus CHOP at week 13, week 20 and week 72 as measured from start of treatment according to the Revised Response Criteria for Malignant Lymphoma.

Protection of trial subjects:

The trial received ethical and regulatory approval, and was run in compliance with the Medicines for Human Use (Clinical Trials) Regulations 2004, and amendments thereafter, the guidelines for Good Clinical Practice, and the applicable policies of the Sponsor, the University of Oxford. Together, these regulations implement the ethical principles of the Declaration of Helsinki (1996) and the regulatory requirements for clinical trials of an investigational medicinal product as set out in the European Union (EU) Directive.

Background therapy:

As well as Ofatumumab, all patients were treated with up to a maximum of six three-weekly cycles of CHOP chemotherapy. This consisted of: cyclophosphamide 750 mg/m2 intravenous (iv) bolus, doxorubicin 50 mg/m2 iv bolus, vincristine 1.4 mg/m2 (maximum 2 mg or 1 mg in patients over 70 years old) iv infusion in 50 ml sodium chloride 0.9% over 10 minutes, prednisolone 40 mg/m2 orally od, on day one and prednisolone 40 mg/ m2 orally od on days 2–5 of each cycle. CHOP chemotherapy is not regarded as an IMP as it is standard care and all patients were treated the same.

Evidence for comparator:

No comparator used - single arm study.

Actual start date of recruitment	27 April 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 43
Worldwide total number of subjects	43
EEA total number of subjects	43

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	19
From 65 to 84 years	21
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

43 patients were recruited across 10 active sites in UK, of which 37 were found to be evaluable (received at least 1 full cycle of treatment and had a response assessment). The first patient was recruited on 05May2011 and the last patient was recruited on 01Dec2014.

Pre-assignment

Screening details:

Screened 48 patients. Eligible if >18, ECOG PS 0-3, known diagnosis of B-CLL and newly diagnosed, untreated and biopsy proven DLBCL Richter's transformation according to WHO classification. Not eligible if previously treated with anthracycline-containing treatment for DLBCL within six months, or have central nervous system involvement with RS/B-CLL

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Baseline

Arm description:

Baseline period

Arm type	Experimental
Investigational medicinal product name	Ofatumumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ofatumumab was infused intravenously on day 1 (300 mg), day 8 (1000 mg) and day 15 (1000mg) in the first cycle, followed by infusions every 3 weeks of 1000 mg on the first day of each cycle for a total of 6 cycles.

Number of subjects in period 1 [1]	Baseline
Started	37
Completed	37

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 43 patients were registered to the trial, but only 37 of these patients were evaluable: evaluable patients must have received at least 1 full cycle of treatment and had a response assessment. If any patients were identified as non-evaluable they were replaced within the recruitment period.

Period 2	
Period 2 title	Induction
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms	
Arm title	Ofatumumab + CHOP

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Ofatumumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ofatumumab was infused intravenously on day 1 (300 mg), day 8 (1000 mg) and day 15 (1000mg) in the first cycle, followed by infusions every 3 weeks of 1000 mg on the first day of each cycle for a total of 6 cycles.

Number of subjects in period 2	Ofatumumab + CHOP
Started	37
Completed	37

Period 3	
Period 3 title	Maintenance
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms	
Arm title	Ofatumumab + CHOP

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Ofatumumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ofatumumab was infused intravenously on day 1 (300 mg), day 8 (1000 mg) and day 15 (1000mg) in the first cycle, followed by infusions every 3 weeks of 1000 mg on the first day of each cycle for a total of 6 cycles.

Number of subjects in period 3	Ofatumumab + CHOP
Started	37
Completed	37

Baseline characteristics

Reporting groups	
Reporting group title	Baseline
Reporting group description:	
All evaluable patients.	

Reporting group values	Baseline	Total	
Number of subjects	37	37	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	18	18	

Stage II	9	9	
Stage III	3	3	
Stage IV	2	2	
Not assessed/documented	1	1	
Binet Staging Units: Subjects			
Clinical stage A	19	19	
Clinical stage B	12	12	
Clinical stage C	6	6	
B-symptoms history			
History of constitutional symptoms (B-symptoms): o Experience of night sweats (without signs of infection) o Unexplained, unintentional weight loss > 10% within the previous 6 months o Experience of extreme fatigue o Recurrent, unexplained fever of greater than 38'C or 100.5'F for 2 weeks			
Units: Subjects			
Yes	22	22	
No	15	15	
Platelet Count Units: Subjects			
< 100 x 10^9/l	10	10	
>100 x 10^9/l	27	27	
Bulk in lymph node over 5 cm Units: Subjects			
Yes	18	18	
No	19	19	
Previous treatments			
Previous treatments of B-CLL			
Units: Subjects			
None	17	17	
One	12	12	
Two or more	8	8	

End points

End points reporting groups

Reporting group title	Baseline
Reporting group description: Baseline period	
Reporting group title	Ofatumumab + CHOP
Reporting group description: -	
Reporting group title	Ofatumumab + CHOP
Reporting group description: -	
Subject analysis set title	Baseline
Subject analysis set type	Full analysis
Subject analysis set description: All evaluable patients have baseline characteristics available.	
Subject analysis set title	Evaluable patients
Subject analysis set type	Intention-to-treat
Subject analysis set description: All patients recruited who received at least one full cycle of CHOP-O and had a response assessment by either clinical examination or CT scan.	
Subject analysis set title	Responders
Subject analysis set type	Intention-to-treat
Subject analysis set description: Responders are those patients with complete remission (CR), partial remission (PR) or complete remission unconfirmed (CRu) at post cycle 6 assessment.	
Subject analysis set title	Non-responders
Subject analysis set type	Intention-to-treat
Subject analysis set description: Non-responders are those patients with stable disease (SD) or progressive disease (PD) at post cycle 6 assessment.	

Primary: Objective response rate

End point title	Objective response rate
End point description: The primary objective of the trial is to determine the objective response rate (ORR) of ofatumumab plus CHOP according to the Revised Response Criteria for Malignant Lymphoma (Cheson criteria) as measured after induction. Patients will be classified as responders/non-responders as follows: complete remission (CR), partial remission (PR) or nodular partial remission (nPR) as responders while stable disease (SD) and progressive disease (PD) as non-responders.	
End point type	Primary
End point timeframe: After cycle 6 of treatment, or if the patient withdraws from treatment earlier than cycle 6, their response recorded at withdrawal will be used. Or if an assessment is not performed at withdrawal, the latest disease response is used (i.e. post cycle 4).	

End point values	Responders	Non-responders		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17	20		
Units: Patients				
number (not applicable)				
Responders	17	0		

Statistical analyses

Statistical analysis title	Objective Response Rate

Statistical analysis description:

Patients are classified as responders/non-responders as follows: complete remission (CR), partial remission (PR) and complete remission unconfirmed (CRu) are classified as responders; while stable disease (SD) and progressive disease (PD) are classified as non-responders. The ORR is reported as the proportion of responders at post cycle 6, including two-sided 95% confidence intervals.

Comparison groups	Non-responders v Responders
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	Objective Response Rate
Point estimate	46
Confidence interval	
level	95 %
sides	2-sided
lower limit	29.7
upper limit	62.2

Notes:

[1] - No formal comparison of the primary end point can be made as there is only one treatment arm.

Secondary: Overall Survival

End point title	Overall Survival

End point description:

End point type	Secondary

End point timeframe:

Length of survival is defined in months as the time from entry into the study until death from any cause. Those who are not observed to die during the course of the trial will be censored at their last known follow-up date.

End point values	Evaluable patients			
Subject group type	Subject analysis set			
Number of subjects analysed	37			
Units: Months				
median (confidence interval 95%)	11.4 (6.4 to 25.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival

End point title	Progression Free Survival

End point description:

End point type	Secondary

End point timeframe:

Length of survival is defined in months as the time from entry into the study until lymphoma progression or death from any cause. Those who are not observed to progress or die during the course of the trial will be censored at their last known progres

End point values	Evaluable patients			
Subject group type	Subject analysis set			
Number of subjects analysed	37			
Units: Months				
median (confidence interval 95%)	6.2 (4.9 to 14)			

Statistical analyses

No statistical analyses for this end point

Secondary: Constitutional symptoms (B-symptoms)

End point title	Constitutional symptoms (B-symptoms)

End point description:

End point type	Secondary

End point timeframe:

Baseline.

End point values	Evaluable patients			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: Patients				
Experience of night sweats	15			
No experience of night sweats	22			
Unexplained weight loss >10% within last 6 months	9			
No unexplained weight loss >10% within last 6 mths	28			
Experience of extreme fatigue	6			
No experience of extreme fatigue	31			
Recurrent, unexplained fever >38 deg's for 2 weeks	4			
No recurrent, unexplained fever >38 for 2 weeks	33			

Statistical analyses

No statistical analyses for this end point

Secondary: ECOG Performance Status

End point title	ECOG Performance Status

End point description:

End point type	Secondary

End point timeframe:

Post cycle 6

End point values	Evaluable patients			
Subject group type	Subject analysis set			
Number of subjects analysed	37			
Units: Patients				
Zero	10			
One	6			
Two	0			
Three	0			
Not assessed/documented	3			
Withdrew prior to assessment	18			

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

Adverse Event Monitoring starts from the time the patient gives informed consent, unless specified otherwise, and until they complete the trial.

Adverse event reporting additional description:

Only AEs of CTCAE grade 3 or grade 4 are reported here.

Assessment type	Systematic

Dictionary used

Dictionary name	NCI-CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	Safety population

Reporting group description:

All patients who received at least one dose of the trial treatment, including those deemed not evaluable for the primary outcome.

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	36 / 43 (83.72%)		
number of deaths (all causes)	28		
number of deaths resulting from adverse events	0		
Investigations			
Neutrophil count decreased			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Soft tissue mass	Additional description: Soft tissue paravertebral mass (necrotic tumour)		
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Adenocarcinoma of colon	Additional description: Adenocarcinoma - Sigmoid Colon		
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			

Fracture			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Thromboembolic event			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Ischaemia	Additional description: Ischaemia cerebrovascular		
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Memory impairment			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			

subjects affected / exposed	7 / 43 (16.28%)		
occurrences causally related to treatment / all	8 / 9		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Unwell	Additional description: Patient looked generally unwell		
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fever			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences causally related to treatment / all	4 / 7		
deaths causally related to treatment / all	0 / 0		
Disease progression			
subjects affected / exposed	7 / 43 (16.28%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 7		
Infusion related reaction			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infusion site extravasation			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			

Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorder	Additional description: Patient unwell overnight, D&V, stomach pains.		
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colonic perforation			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary fibrosis			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Endocarditis	Additional description: Endocarditis infective		
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Infection			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Lung infection			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 1		
Neutropenic sepsis			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Parainfluenzae virus infection			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	5 / 43 (11.63%)		
occurrences causally related to treatment / all	8 / 8		
deaths causally related to treatment / all	0 / 1		
Skin infection			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Tumour lysis syndrome			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 1		

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

Non-serious adverse events	Safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 43 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon	Additional description: Adenocarcinoma of sigmoid colon unrelated to the trial treatment.		
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Soft tissue mass	Additional description: Soft tissue paravertebral mass (necrotic tumor)		
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Vascular disorders			
Thromboembolic event			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences (all)	2		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Fever			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences (all)	4		
Infusion related reaction			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences (all)	2		
Malaise			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Other	Additional description: Fever and diarrhoa - treated as neutropenic sepsis with antibiotics however was not septic.		
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			

Bronchiectasis			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Aspiration			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Pleural effusion			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Investigations			
Neutrophil count decreased			
subjects affected / exposed	8 / 43 (18.60%)		
occurrences (all)	10		
Platelet count decreased			
subjects affected / exposed	2 / 43 (4.65%)		

Abdominal pain			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Anal pain			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Colonic perforation			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Gastrointestinal disorder			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Hyperhidrosis			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Rash maculo-papular			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Urticaria			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Renal and urinary disorders			
Cystitis noninfective			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			

Pain in extremity			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Infections and infestations			
Infection			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	3		
Lower respiratory tract infection			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	3		
Parainfluenzae virus infection			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Anorectal infection			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Endocarditis			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Lung infection			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences (all)	4		
Sepsis			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences (all)	7		
Skin infection			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Tooth infection			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 February 2011	Substantial Amendment 001: Addition of new sites – Kings College Hospital and UCLH
30 March 2011	Substantial Amendment 002: Addition of new site – Nottingham, Removal of existing site – Queen Elizabeth Hospital
13 June 2011	Substantial Amendment 003: PIS update
17 June 2011	Substantial Amendment 004: Addition of a new site – Queen Elizabeth Hospital, Birmingham
26 October 2011	Substantial Amendment 005: Addition of questionnaire booklets
24 April 2012	Substantial Amendment 006: Addition of a new site – Royal Marsden Hospital London
09 July 2012	Substantial Amendment 007: Change of drug distribution centre – from Aptuit to Catalent
30 April 2013	Substantial Amendment 008: PIS update
02 September 2013	Substantial Amendment 009: Protocol update: change to exclusion criteria, timing of assessments and SAE criteria.
22 January 2014	Substantial Amendment 010: Change of PI at Royal Bournemouth Hospital
16 July 2014	Substantial Amendment 011: PIS update
31 October 2014	Substantial Amendment 012: Protocol update: addition of list of adverse events, clarification of 'objective response', changes to contact information GP Letter update, IB update

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.

The data is not compared in a prospective randomized clinical trial. The small number of patients is one limitation, and unfortunately, only limited data of sufficient quality were available for a number of endpoints, meaning no formal analyses.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27378086