Clinical trial results:
A pilot study to establish the safety and efficacy of a combination of dexamethasone and lenalidomide in patients with relapsed or refractory chronic lymphocytic leukaemia (CLL)

Summary

EudraCT number	2010-024520-15
Trial protocol	GB
Global end of trial date	01 February 2016

Results information

Result version number	v1 (current)
This version publication date	16 July 2017
First version publication date	16 July 2017

Trial information

Trial identification

Sponsor protocol code	UCL/09/0387

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01459211
WHO universal trial number (UTN)	-
Other trial identifiers	Celgene study code: RV-CLL-PI-0569

Notes:

Sponsors

Sponsor organisation name	University College London
Sponsor organisation address	Joint Research Office, Gower Street, London, United Kingdom, WC1e 6BT
Public contact	ctc.sponsor@ucl.ac.uk, Cancer Research UK and UCL Cancer Trials Centre, 44 2076799898, ctc.sponsor@ucl.ac.uk
Scientific contact	ctc.sponsor@ucl.ac.uk, Cancer Research UK and UCL Cancer Trials Centre, 44 2076799898, ctc.sponsor@ucl.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	01 February 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 February 2015
Global end of trial reached?	Yes
Global end of trial date	01 February 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The aim of this study is to establish the safety and efficacy of a combination of dexamethasone and lenalidomide (Revlimid®) (D+L) in subjects with relapsed or refractory CLL who have failed or are unable to tolerate standard up-front therapy with regimens containing Fludarabine or, in those with mutations in the p53 gene, CAMPATH-1H.

The primary endpoints are:
1. Proportion of patients who achieve objective response (CR + PR) according to the updated 1996 NCIWG criteria measured at 4 weeks after the completion of chemotherapy
2. Proportion of patients suffering Grade III/IV toxicity as assessed by the NCI Common Terminology Criteria for Adverse Events (version 4.03) including an assessment of the frequency of tumour flare reactions

Protection of trial subjects:

Patients underwent screening evaluations to confirm eligibility for the trial, including: full medical history, physical examination, full blood count & biochemistry tests, thyroid function tests, serum immunoglobulins, infection screen for HIV and Hepatitis B & C & ECG. Cytogenetic analyses & bone marrow biopsy confirmed diagnosis. Patients with renal impairment at baseline started on a reduced lenalidomide dose.

Patients were monitored for haematological toxicities, such as thrombocytopenia and neutropenia. Full blood counts are checked regularly during each cycle, particularly for the first three cycles of treatment. The protocol provided instructions for dose delays or reductions. G-CSF was recommended for patients with severe neutropenia.

Patients were assessed regularly during treatment and the trial protocol provided appropriate guidance for the treatment of tumour lysis syndrome and tumour flare reaction, as well as subsequent dose reductions. Dose modifications were provided for other toxicities including neuropathy, hyperthyroidism, hypothyroidism, renal & hepatic impairment, thromboembolic events and rashes.

The protocol gave recommendations for supportive care, including prophylaxis against pneumocystis pneumonia, herpes simplex and varicella zoster reactivation, antifungal agents, antiemetics, corticosteroid prophylaxis to avoid infusion-related reactions and transfusion of blood and blood products and antibiotics as appropriate.

Due to lenalidomide's structural relationship with thalidomide (known to cause life threatening birth defects), the Celgene Risk Minimisation Plan to prevent pregnancy was observed in the trial. All participants were counselled concerning the risks & agreed to a schedule of pregnancy testing and use of contraception, dependent on their sex and childbearing potential, in order to enter the study. Further counselling & monitoring of the pregnancy status of participant and/or partner were required throughout the study.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable - no comparator used

Actual start date of recruitment	01 March 2012
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: 12
Worldwide total number of subjects	12
EEA total number of subjects	12

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)	6
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 12 patients were recruited at two UK sites between November 2012 and May 2014.

Pre-assignment

Screening details:

Screening investigations included physical assessments and disease status evaluation.

A total of 17 patients were screened for the study. Patients were not entered onto the trial due to patient refusal rather than failure of screening examinations.

Period 1

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

Blinding implementation details:

n/a

Arms

Arm title	Lenalidomide and Dexamethasone

Arm description:

Patients received up to twelve 28-day cycles of treatment. Each cycle consisted of:
1. Oral Dexamethasone (20mg daily, days 1-4),
2. Oral Lenalidomide on days 1-28 of each cycle, starting at 5mg per day in cycle 1 in patients with creatinine clearance ≥ 50ml/min calculated by Cockcroft-Gault. Dose increased to 10mg per day with cycles 2-12 unless there was evidence of disease progression or unacceptable drug toxicity. Patients with renal impairment (creatinine clearance ≥ 30ml/min but < 50ml/min) were started on 2.5mg/day in cycle 1, increasing to 5mg/day in subsequent cycles.

Lenalidomide was interrupted with any grade 3-4 toxicity and recommenced at a dose 2.5mg lower than previously once toxicity had resolved.

Treatment was discontinued upon disease progression or with unacceptable drug toxicity.

Arm type	Experimental
Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	Revlimid
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Lenalidomide should be taken day 1 -28 of each cycle.

5 mg/day in cycle 1, increased to 10 mg/day for cycles 2 - 12 in the absence of toxicity.
If a patient demonstrated renal impairment (creatinine clearance ≥ 30ml/min but < 50ml/min) start dose was 2.5 mg/day for the first cycle and increased to 5 mg/day.

Lenalidomide capsules were taken at approximately the same time each day. The capsules were not opened, broken or chewed. The capsules were swallowed whole, preferably with water, either with or without food.

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

20 mg/day for days 1-4 per cycle only.

Dexamethasone was taken by mouth. Tablets swere swallowed whole with water. Tablets were not crushed or chewed.

Number of subjects in period 1	Lenalidomide and Dexamethasone
Started	12
Start of cycle 2	9
Start of cycle 3	7
Start of cycle 4	6
Start of cycle 5	5
Start of cycle 6	5
Start of cycle 7	3
Start of cycle 8	3
Start of cycle 9	3
Start of cycle 10	3
Start of cycle 11	3
Start of cycle 12	3
Completed	3
Not completed	9
Adverse event, serious fatal	1
Physician decision	1
Adverse event, non-fatal	3
Lack of efficacy	4

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	12	12	
Age categorical			
Age			
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)	6	6	
From 65-84 years	6	6	
85 years and over	0	0	
Gender categorical			
Gender			
Units: Subjects			
Female	0	0	
Male	12	12	
WHO performance status			
WHO performance status at registration			
Units: Subjects			
Grade 0	6	6	
Grade 1	4	4	
Grade 2	2	2	
IgVH mutational analysis			
CLL patients can be divided into 2 basic groups on the basis of the mutational status of the immunoglobulin heavy-chain variable-region (IgVH) gene in leukemic cells: patients with IgVH gene mutations have longer survival than those without.			
Units: Subjects			
Mutated	0	0	
Unmutated	9	9	
Missing/Not known	3	3	
Lymphadenopathy/CLL			
The presence of lymphadenopathy/CLL in the lymph nodes visible on CT scan.			
Units: Subjects			
Lymphadenopathy present	12	12	
Bone marrow assessment			
The presence of disease in the bone marrow			
Units: Subjects			
Aspirate and trephine involvement	12	12	
Disease assessment (modified 3-stage			

system) Units: Subjects			
Low risk	1	1	
Intermediate risk	1	1	
High risk	10	10	
Previous lines of treatment			
No of previous lines of treatment each patient had			
Units: Number median full range (min-max)	 5 2 to 9	 -	
Haemoglobin Units: g/dl median full range (min-max)	 11.9 9.6 to 17.6	 -	
Neutrophil count Units: x10^9/l median full range (min-max)	 5.9 0.1 to 18.4	 -	
White blood cell count Units: x10^9/l median full range (min-max)	 42.6 2.4 to 167.3	 -	
Lymphocyte count Units: x10^9/l median full range (min-max)	 33.4 1.8 to 155.6	 -	
Platelet count Units: x10^9/l median full range (min-max)	 117.5 12 to 225	 -	
Monocyte count Units: x10^9/l median full range (min-max)	 0.8 0 to 3.9	 -	

End points

End points reporting groups

Reporting group title	Lenalidomide and Dexamethasone

Reporting group description:

Patients received up to twelve 28-day cycles of treatment. Each cycle consisted of:
1. Oral Dexamethasone (20mg daily, days 1-4),
2. Oral Lenalidomide on days 1-28 of each cycle, starting at 5mg per day in cycle 1 in patients with creatinine clearance ≥ 50ml/min calculated by Cockcroft-Gault. Dose increased to 10mg per day with cycles 2-12 unless there was evidence of disease progression or unacceptable drug toxicity. Patients with renal impairment (creatinine clearance ≥ 30ml/min but < 50ml/min) were started on 2.5mg/day in cycle 1, increasing to 5mg/day in subsequent cycles.

Lenalidomide was interrupted with any grade 3-4 toxicity and recommenced at a dose 2.5mg lower than previously once toxicity had resolved.

Treatment was discontinued upon disease progression or with unacceptable drug toxicity.

Primary: Overall response rate

End point title	Overall response rate[1]

End point description:

Proportion of patients who achieve objective response (CR+PR) according to the updated 1996 NCIWG criteria measured at 4 weeks after the completion of chemotherapy.

End point type	Primary

End point timeframe:

Measured 4 weeks after last treatment administration.

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 primary endpoint represents numbers of patients achieving a response. No specific statistical analysis is necessary to establish numbers of patients. Furthermore, due to the small sample size, statistical analysis would not be possible.

End point values	Lenalidomide and Dexamethasone			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Number of patients achieving response				
Complete response	0			
Partial response	3			
Stable disease	2			
Progressive disease	5			
Not assessable	2			

Statistical analyses

No statistical analyses for this end point

Primary: Toxicity

End point title	Toxicity[2]

End point description:

Proportion of patients suffering grade 3 or 4 toxicity (excluding neutropenia) as assessed by the NCI Common Terminology Criteria for Adverse Events (Version 4.03) including an assessment of the frequency of tumour flare reactions.

End point type	Primary

End point timeframe:

From start of treatment until patient withdrew from treatment or completed all chemotherapy cycles.

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: This primary endpoint is the proportion of patients suffering grade 3 or 4 adverse events. No specific statistical analysis is necessary to establish the percentage of patients. This can be calculated using the numbers of patients on the trial and number suffering grade 3 or 4 adverse events. Furthermore, due to the small sample size, statistical analysis would not be possible.

End point values	Lenalidomide and Dexamethasone			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Percentage	92			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response

End point title	Duration of response

End point description:

For patients who achieve objective response, duration of response is defined as time from the first date of a confirmed disease response to the first date of diagnosis of progressive disease or death due to any cause. Censoring will occur on the date of last study assessment with non-missing response.

End point type	Secondary

End point timeframe:

From the date of the patient's first objective response in the study to the date of progression or death.

End point values	Lenalidomide and Dexamethasone			
Subject group type	Reporting group			
Number of subjects analysed	4[3]			
Units: Months				
median (full range (min-max))	3.3 (1.9 to 10.3)			

Notes:

[3] - Four patients achieved a partial response during the study and subsequently progressed.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to next treatment

End point title	Time to next treatment

End point description:

Time to next treatment is defined as time from the date of trial registration to the date of next non-protocol treatment or death due to any cause.

End point type	Secondary

End point timeframe:

During the follow-up of patients after the completion/termination of their study treatment.

End point values	Lenalidomide and Dexamethasone			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: months				
median (full range (min-max))	6.6 (0.9 to 15.2)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events that occurred between informed consent and 30 days post last trial treatment administration were reported.

Adverse event reporting additional description:

Adverse events were recorded in the patient notes and reported to the coordinating centre via the trial CRFs. Those meeting the definition of a Serious Adverse Event (SAE) were reported using the trial specific SAE Report. Causality assessment to study IMPs was performed by site investigator and/or study CI.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.03

Reporting groups

Reporting group title	Lenalidomide and Dexamethasone

Reporting group description:

Twelve 28-day cycles of treatment. Each cycle will consist of:
1. Oral Dexamethasone (20mg daily, days 1-4),
2. Oral Lenalidomide on days 1-28 of each cycle, starting at 5mg per day in cycle 1 in patients with creatinine clearance ≥ 50ml/min calculated by Cockcroft-Gault. The dose will be increased to 10mg per day with cycles 2-12 unless there is evidence of disease progression or unacceptable drug toxicity. Patients with renal impairment at baseline are started on 2.5 mg/day in cycle 1, increasing to 5 mg/day in subsequent cycles.

Serious adverse events	Lenalidomide and Dexamethasone		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 12 (75.00%)		
number of deaths (all causes)	7		
number of deaths resulting from adverse events	1		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colonic perforation			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Respiratory, thoracic and mediastinal disorders			
Hiccups			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Febrile neutropenia			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Infection of unknown source			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Lung infection	Additional description: (includes reported event term lower respiratory infection)		
subjects affected / exposed	3 / 12 (25.00%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Bladder infection			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Lenalidomide and Dexamethasone		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 12 (100.00%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Thromboembolic event			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
General disorders and administration site conditions			
Aggression	Additional description: Not a CTCAE term		
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Non-cardiac chest pain			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Cramp	Additional description: Not a CTCAE term		
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	3		
Decreased appetite	Additional description: Not a CTCAE term		
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	3		
Edema limbs			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	4		
Fatigue			
subjects affected / exposed	10 / 12 (83.33%)		
occurrences (all)	22		
Fever			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Flu-like symptoms			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Gout	Additional description: Not a CTCAE term		

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Immune system disorders			
Allergic reaction			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Genital edema			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	4		
Dyspnea			
subjects affected / exposed	7 / 12 (58.33%)		
occurrences (all)	13		
Productive cough			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Psychiatric disorders			
Confusion			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	3		
Mania			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Insomnia			
subjects affected / exposed	6 / 12 (50.00%)		
occurrences (all)	7		
Mood swings	Additional description: Not a CTCAE term		
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Investigations			
Aspartate aminotransferase increased			

subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	7		
Alanine aminotransferase increased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Creatinine increased			
subjects affected / exposed	6 / 12 (50.00%)		
occurrences (all)	19		
Decreased immunoglobulins	Additional description: Not a CTCAE term		
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Urea elevated	Additional description: Not a CTCAE term		
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Blood bilirubin increased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Weight loss			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	4		
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	5		
Headache			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Peripheral (sensory/motor) neuropathy	Additional description: Not a CTCAE term		
subjects affected / exposed	4 / 12 (33.33%)		
occurrences (all)	7		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 12 (41.67%)		
occurrences (all)	8		
Neutropenia			

subjects affected / exposed	9 / 12 (75.00%)		
occurrences (all)	24		
Platelet count decreased			
subjects affected / exposed	9 / 12 (75.00%)		
occurrences (all)	32		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	6 / 12 (50.00%)		
occurrences (all)	19		
Diarrhoea			
subjects affected / exposed	6 / 12 (50.00%)		
occurrences (all)	19		
Heartburn	Additional description: Not a CTCAE term		
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Hiccups			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	5 / 12 (41.67%)		
occurrences (all)	7		
Stomach pain			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
PR bleeding	Additional description: not a CTCAE term		
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Rash	Additional description: Not a CTCAE term		
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	3		
Renal and urinary disorders			

Haematuria			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Urinary incontinence			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Renal and urinary disorders - other			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Generalised muscle weakness			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Myalgia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Infections and infestations			
Chest infection	Additional description: Not a CTCAE term		
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	3		
Upper respiratory tract infection	Additional description: Not a CTCAE term		
subjects affected / exposed	4 / 12 (33.33%)		
occurrences (all)	4		
Lung infection			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Papulopustular rash			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Rhinitis infection			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Sepsis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Tooth infection			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Urinary tract infection			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hypernatraemia			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Hypocalcaemia			
subjects affected / exposed	6 / 12 (50.00%)		
occurrences (all)	8		
Hypokalaemia			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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.

Following discussions with the trial management group, the LenD study was closed to recruitment on the 12th December 2014 due to continuing poor recruitment. There were no necessary changes to the protocol. Patients were continued to be followed up.

Notes: