Clinical trial results:
A single arm open labeled multicentre phase 1b dose escalation study of carfilzomib taken in combination with Thalidomide and Dexamethasone in relapsed AL amyloidosis (CATALYST trial).

Summary

EudraCT number	2015-000954-40
Trial protocol	
Global end of trial date	21 October 2019

Results information

Result version number	v1 (current)
This version publication date	
First version publication date	

Trial information

Trial identification

Sponsor protocol code	14/0786

Additional study identifiers

ISRCTN number	ISRCTN16308011
ClinicalTrials.gov id (NCT number)	NCT02545907
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University College London
Sponsor organisation address	Joint Research Office, UCL, Gower St, London, United Kingdom, WC1E 6BT
Public contact	Regulatory Affairs and Governance Manager, CTRU QA Department, +44 01133439077, medctruq@leeds.ac.uk
Scientific contact	Regulatory Affairs and Governance Manager, CTRU QA Department, +44 01133439077, medctruq@leeds.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	26 September 2019

Is this the analysis of the primary completion data?	Yes
Primary completion date	19 March 2019
Global end of trial reached?	Yes
Global end of trial date	21 October 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

During the dose escalation phase, the purpose of the study is to determine the maximum tolerated and recommended doses of carfilzomib when given with set doses of thalidomide and dexamethasone, and to assess the safety and toxicity of this combination of drugs when given to patients with AL amyloidosis. During the dose expansion phase, the primary purpose is to further assess the safety and tolerability of the combination of carfilzomib at the recommended dose (found in the escalation phase) combined with set doses of thalidomide and dexamethasone.

Protection of trial subjects:

In conducting the trial, the Sponsor, LEEDS CTRU and sites complied with all laws and statutes, as amended from time to time, applicable to the performance of clinical trials including, but not limited to:
• the principles of ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95) as set out in Schedule 1 (Conditions and Principles of Good Clinical Practice and for the Protection of Clinical Trial Subjects) of the Medicines for Human Use (Clinical Trials) Regulations 2004 and the GCP Directive 2005/28/EC, as set out in SI 2006/1928
• Human Rights Act 1998
• Data Protection Act 1998
• Freedom of Information Act 2000
• Human Tissue Act 2004
• Human Tissue Act (Scotland) 2006
• Medicines Act 1968
• Medicines for Human Use (Clinical Trials) UK Regulations SI 2004/1031, and subsequent amendments
• Good Manufacturing Practice
• the Research Governance Framework for Health and Social Care, issued by the UK Department of Health (Second Edition 2005) or the Scottish Health Department Research Governance Framework for Health and Community Care (Second Edition 2006).

Trial data collected on paper was sent to the CTRU and filed in locked filing cabinets. Data entered onto a trial database application, MACRO is stored on a private network protected by a firewall. Access to the database is restricted to trials staff by login and password.

All information collected during the course of the trial was kept strictly confidential. All data collection forms, except consent forms, that were transferred to or from the CTRU were coded with a trial number and included two patient identifiers, usually the patient's initials and date of birth. Information was held securely on paper and electronically at the CTRU, including appropriate storage, restricted access and disposal arrangements of patient personal and clinical details. Participants were not identified in the results of the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 September 2017
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: 11
Worldwide total number of subjects	11
EEA total number of subjects	11

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	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first centre opened to recruitment in the UK on 27th July 2017 and the first participant was registered on 11th September 2017. Recruitment closed on 31st January 2019.

Pre-assignment

Screening details:

11 participants were registered to the study, 10 of which were eligible and received trial treatment.

Pre-assignment period milestones

Number of subjects started	11
Number of subjects completed	10

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Protocol deviation: 1

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	Dose level 0

Arm description:

Participants received 36mg/m^2 of Carfilzomib on days 1, 8 and 15 for up to 6 cycles. All participants received a 20mg/m^2 loading dose of Carfilzomib on day 1 of cycle 1.

Arm type	Experimental
Investigational medicinal product name	Carfilzomib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Lyophilized Carfilzomib for Injection. Composition: Lyophilized parenteral drug product in 60 mg single use vials. Upon reconstitution, Carfilzomib for injection consists of 2 mg/mL solution.

Participants received 36mg/m^2 of Carfilzomib on days 1, 8 and 15 for up to 6 cycles. All participants received a 20mg/m^2 loading dose of Carfilzomib on day 1 of cycle 1.

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

Dosage and administration details:

20mg of dexamethasone on days 1, 8 and 15 for up to 6 cycles.

Investigational medicinal product name	Thalidomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

50mg of Thalidomide on days 1- 28 for up to 6 cycles.

Arm title	Dose level 1

Arm description:

Participants received 45mg/m^2 of Carfilzomib on days 1, 8 and 15 for up to 6 cycles. All participants received a 20mg/m^2 loading dose of Carfilzomib on day 1 of cycle 1.

Arm type	Experimental
Investigational medicinal product name	Carfilzomib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Lyophilized Carfilzomib for Injection. Composition: Lyophilized parenteral drug product in 60 mg single use vials. Upon reconstitution, Carfilzomib for injection consists of 2 mg/mL solution.

Participants received 45mg/m^2 of Carfilzomib on days 1, 8 and 15 for up to 6 cycles. All participants received a 20mg/m^2 loading dose of Carfilzomib on day 1 of cycle 1.

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

Dosage and administration details:

20mg of dexamethasone on days 1, 8 and 15 for up to 6 cycles.

Investigational medicinal product name	Thalidomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

50mg of Thalidomide on days 1- 28 for up to 6 cycles.

Number of subjects in period 1[1]	Dose level 0	Dose level 1
Started	3	7
Completed	2	5
Not completed	1	2
Adverse event, non-fatal	1	2

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: 11 participants were registered to the study, 10 of which were eligible and received trial treatment.

Baseline characteristics

Reporting groups	
Reporting group title	Dose level 0
Reporting group description:	
Participants received 36mg/m^2 of Carfilzomib on days 1, 8 and 15 for up to 6 cycles. All participants received a 20mg/m^2 loading dose of Carfilzomib on day 1 of cycle 1.	
Reporting group title	Dose level 1
Reporting group description:	
Participants received 45mg/m^2 of Carfilzomib on days 1, 8 and 15 for up to 6 cycles. All participants received a 20mg/m^2 loading dose of Carfilzomib on day 1 of cycle 1.	

Reporting group values	Dose level 0	Dose level 1	Total
Number of subjects	3	7	10
Age categorical Units: Subjects			
Adults (18-64 years)	1	5	6
From 65-84 years	2	2	4
Gender categorical Units: Subjects			
Female	1	5	6
Male	2	2	4
Number of lines of previous therapy Units: Subjects			
One	0	3	3
Two	2	2	4
Three	1	1	2
Four	0	1	1
ECOG Performance status Units: Subjects			
Zero	0	2	2
One	3	4	7
Two	0	1	1
Time from original AL amloidosis diagnosis to baseline Units: Years			
arithmetic mean	7.8	3.2	
standard deviation	± 3.87	± 1.8	-
Time from most recent relapse to baseline			
There are 4 (2 at dose level 0, 2 at dose level 1) participants with refractory disease, thus time from most recent relapse is not applicable to these patients.			
Units: Years			
median	0.8	0.9	
full range (min-max)	0.8 to 0.8	0.2 to 2.0	-
Creatinine Units: umol/L			
arithmetic mean	102	90.7	
standard deviation	± 38.0	± 55.5	-
eGRF			

Units: mL/min			
arithmetic mean	67.3	69.6	
standard deviation	± 30.2	± 28.5	-
NT Pro-BNP			
Units: pmol/L			
arithmetic mean	29.9	90.1	
standard deviation	± 21.9	± 90.3	-
dFLC			
Units: dFLC			
arithmetic mean	102	135	
standard deviation	± 84.7	± 157	-
Kappa-Lambda Ratio			
Units: Ratio			
arithmetic mean	0.2	11.1	
standard deviation	± 0.19	± 24.6	-

End points

End points reporting groups

Reporting group title	Dose level 0
Reporting group description:	
Participants received 36mg/m^2 of Carfilzomib on days 1, 8 and 15 for up to 6 cycles. All participants received a 20mg/m^2 loading dose of Carfilzomib on day 1 of cycle 1.	
Reporting group title	Dose level 1
Reporting group description:	
Participants received 45mg/m^2 of Carfilzomib on days 1, 8 and 15 for up to 6 cycles. All participants received a 20mg/m^2 loading dose of Carfilzomib on day 1 of cycle 1.	

Primary: Dose-limiting toxicities

End point title	Dose-limiting toxicities[1]

End point description:

This will establish the maximum tolerated dose and recommended dose of carfilzomib in combination with thalidomide and dexamethasone.

Three evaluable participants were recruited to dose level with no dosing limiting toxicities (DLTs) observed. A further 3 evaluable participants were recruited in dose level 1, of which one participant experienced a DLT (acute kidney injury). Hence, a further 3 participants were recruited at this dose level. One participant had an SAE following the loading dose (20mg/m2) of carfilzomib and was deemed not evaluable for DLT assessment as they received no further treatment. Three further participants were recruited at dose level 1 with no further DLTs.
There was not appetite within the safety review committee to pursue further cohorts at dose level 2 based upon safety data within the trial. Dose level 1 (Carfilzomib 45mg/m2) was declared the recommended dose (RD).

End point type	Primary

End point timeframe:

Time of receiving first registered dose of carfilzomib in cycle 1 and day 1 cycle 2.

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 simply the number of participants who experienced dose limiting toxicities, no statistical analysis is required.

End point values	Dose level 0	Dose level 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	6[2]		
Units: Number of participants experiencing DLTs				
Experienced DLT	0	1		
Did not experience DLT	3	5		

Notes:

[2] - One patient had a DLT after loading dose of carfilzomib and was deemed not evaluable for the MTD.

Statistical analyses

No statistical analyses for this end point

Primary: Proportion of participants treated who experience any grade 3 or 4 CTCAE toxicity

End point title	Proportion of participants treated who experience any grade 3 or 4 CTCAE toxicity[3]

End point description:

The proportion of patients treated who experience any grade 3 or 4 CTCAE toxicity will be calculated as number of patients who experience any grade 3 or 4 CTCAE toxicity throughout their treatment cycle.

End point type	Primary

End point timeframe:

Throughout all treatment cycles

Notes:

[3] - 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 simply the proportion of participants who experienced any grade 3 or 4 CTCAE toxicity, no statistical analysis is required.

End point values	Dose level 0	Dose level 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	7		
Units: Participants				
Experienced an AE of grade 3 or 4	2	3		
Did not experience an AE of grade 3 or 4	1	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Clonal response rate

End point title	Clonal response rate

End point description:

Number of participants who achieve at least a partial response as per the timeframes above.

End point type	Secondary

End point timeframe:

Within 3 cycles of treatment, at the end of cycle 3, within 6 cycles of treatment and at the end of cycle 6.

End point values	Dose level 0	Dose level 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	7		
Units: Participants				
Within 3 cycles	1	5		
At the end of cycle 3	1	5		
Within 6 cycles	2	5		
At the end of cycle 6	2	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Amyloidotic organ response

End point title	Amyloidotic organ response

End point description:

Amyloidotic organ response rate is defined as the proportion of patients who achieve organ response within 3 months and within 6 months of trial registration.

End point type	Secondary

End point timeframe:

Assessed at post cycle 3 NAC visit and at follow-up (6 months post-registration).

End point values	Dose level 0	Dose level 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	7		
Units: Participants				
Achieved organ response	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of deaths

End point title	Number of deaths

End point description:

End point type	Secondary

End point timeframe:

6 months post-registration

End point values	Dose level 0	Dose level 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	7		
Units: Participants				
Number of deaths	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants progression free

End point title	Number of participants progression free

End point description:

End point type	Secondary

End point timeframe:

6 months post-registration

End point values	Dose level 0	Dose level 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	7		
Units: Participants				
Number of participants who have not progressed	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum response

End point title	Maximum response

End point description:

End point type	Secondary

End point timeframe:

Within 6 months post-registration

End point values	Dose level 0	Dose level 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	7		
Units: Participants				
No response	1	2		
Partial response	0	1		
Very good partial response	2	1		
Complete response	0	3		

Statistical analyses

No statistical analyses for this end point

Secondary: KTD compliance

End point title	KTD compliance

End point description:

Patients will be regarded as compliant to treatment where treatment is received as per protocol until withdrawal from treatment and have no more than 1 dose omission of Carfilzomib, 5 of Thalidomide or 1 of Dexamethasone during each cycle.

End point type	Secondary

End point timeframe:

During treatment

End point values	Dose level 0	Dose level 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	7		
Units: Participants				
KTD compliant	1	5		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

30 days post last trial treatment administration

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	4

Reporting groups

Reporting group title	Dose cohort 0 (36mg/m^2) safety population

Reporting group description:

All participants in dose cohort 0 who have received at least one dose of Carfilzomib and with no protocol deviations with relevant impact on safety.

Reporting group title	Dose cohort 1 (45mg/m^2) safety population

Reporting group description:

All participants in dose cohort 1 who have received at least one dose of Carfilzomib and with no protocol deviations with relevant impact on safety.

Serious adverse events	Dose cohort 0 (36mg/m^2) safety population	Dose cohort 1 (45mg/m^2) safety population	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	2 / 7 (28.57%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
General disorders and administration site conditions			
Fever	Additional description: Patient completed C1 D1 of trial treatment yesterday afternoon. Sent home well. Last night, patient developed T= 40oC. Took herself up to nearest A&E. Kept in hospital for observation		
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal Pain	Additional description: Sudden onset abdo pain requiring admission to hospital. Pyelonephritis with proteus mirabilis complicating left chronic ? obstruction		
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury	Additional description: Admitted through acute oncology services with above symptoms. Admitted for assessment (fludi restriction, bloods, left leg doppler, MSU, stool sample). PAtient was discharged on the 15/08/18 when rena		
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to	0 / 0	1 / 1	

treatment / all			
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Dose cohort 0 (36mg/m^2) safety population	Dose cohort 1 (45mg/m^2) safety population	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	7 / 7 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 3 (66.67%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Hypotension			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Social circumstances			
Social circumstances - Other, specify			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Edema face			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Edema limbs			
subjects affected / exposed	2 / 3 (66.67%)	5 / 7 (71.43%)	
occurrences (all)	2	5	
Edema trunk			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	1 / 3 (33.33%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Gait disturbance			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	
occurrences (all)	1	0	

Fever			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Psychiatric disorders - Other, specify			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Restlessness			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Vascular access complication			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Investigations			
Alkaline phosphatase increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Blood Bilirubin Increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Creatinine increased			
subjects affected / exposed	1 / 3 (33.33%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Ggt Increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	

Urine output decreased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Cardiac disorders			
Heart failure			
subjects affected / exposed	1 / 3 (33.33%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Sinus tachycardia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	1 / 3 (33.33%)	2 / 7 (28.57%)	
occurrences (all)	1	2	
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Dyspnea			
subjects affected / exposed	1 / 3 (33.33%)	2 / 7 (28.57%)	
occurrences (all)	2	2	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 3 (33.33%)	2 / 7 (28.57%)	
occurrences (all)	1	2	
Headache			
subjects affected / exposed	0 / 3 (0.00%)	2 / 7 (28.57%)	
occurrences (all)	0	2	
Lethargy			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	3	
Nervous system disorders - Other, specify			
subjects affected / exposed	0 / 3 (0.00%)	2 / 7 (28.57%)	
occurrences (all)	0	2	
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 3 (33.33%)	1 / 7 (14.29%)	

occurrences (all)	2	1	

Eye disorders			
Blurred Vision			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Bloating			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	0 / 3 (0.00%)	2 / 7 (28.57%)	
occurrences (all)	0	2	
Diarrhea			
subjects affected / exposed	1 / 3 (33.33%)	2 / 7 (28.57%)	
occurrences (all)	1	2	
Mucositis oral			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	1 / 3 (33.33%)	2 / 7 (28.57%)	
occurrences (all)	1	2	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 3 (0.00%)	2 / 7 (28.57%)	
occurrences (all)	0	2	
Renal and urinary disorders - Other, specify			
subjects affected / exposed	1 / 3 (33.33%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	

Pruritus			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Rash maculo-papular			
subjects affected / exposed	1 / 3 (33.33%)	1 / 7 (14.29%)	
occurrences (all)	1	2	
Skin and subcutaneous tissue disorders - Other, specify			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 3 (0.00%)	3 / 7 (42.86%)	
occurrences (all)	0	4	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Hypocalcemia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 7 (28.57%)	
occurrences (all)	0	2	
Hypophosphatemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Infections and infestations			
Bladder Infection			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Infections and infestations - Other, specify			
subjects affected / exposed	1 / 3 (33.33%)	1 / 7 (14.29%)	
occurrences (all)	2	1	
Upper respiratory infection			
subjects affected / exposed	1 / 3 (33.33%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Urinary Tract Infection			
subjects affected / exposed	1 / 3 (33.33%)	0 / 7 (0.00%)	
occurrences (all)	1	0	

Vaginal infection subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 7 (14.29%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 April 2016	This amendment was due to the addition of the Royal Free Hospital (The Royal Free London NHS Foundation Trust; PI Dr Ashutosh Wechalekar) as a site participating in the trial.
04 November 2016	The substantial amendment included the following updated trial-related documents: Protocol v2.0, 22nd September 2016 Protocol v2.0 , 22nd September 2016 _tracked changes IB for Carfilzomib v16.0, 25th September 2015 IB for Carfilzomib v16.1, 16th January 2016 Patient Information Sheet / ICF v3.0, 22nd September 2016 Patient Information Sheet / ICF v3.0, 22nd September 2016 _tracked changes Participant Summary v2.0, 22nd September 2016 Participant Summary v2.0, 22nd September 2016 _tracked changes Thalidomide SmPC 27th July 2016 Dexamethasone SmPC 26th August 2016. There is no impact to the trial from the new information included in this updated SmPC. Updated MHRA Products Form (EudraCT Form) to notify you of the change of Sponsor contact details and authorised representative organisation contact details. Proof of payment for amendment Substantial amendment form to summarise all the changes and to notify you of the addition of a research site and the change of a PI at an existing research site. A form which highlights a summary of the changes made to the protocol, PIS, and other associated documentation. IB summary of changes documents.
23 January 2017	This amendment was to correct the entry of participating sites to Research Sites, rather than Participant Identification Centres (as previously listed on the original IRAS form in Part C).
08 June 2017	This amendment included a change to the importer of the study drug Carfilzomib from Fisher Clinical Services UK Ltd to Amgen Europe. Updated details on the importer of the study drug were added to Annex 1 in section D9-2. Also enclosed was a cross reference letter provided from AMGEN to the MHRA, dated 07 April 2017 regarding this amendment. Details of the Manufacturing Authorisation for Investigational Medicinal Products (MIA (IMP)) for the Amgen Breda site (authorisation number 108520 F) from the EMA's EudraGMDP database was also enclosed. The MIA (IMP) authorised the Amgen Breda site to conduct the activities of importation, labelling, packaging and QP release of carfilzomib. Additionally, a copy of the Amgen QP statement, supporting release of the carfilzomib with respect to the CATALYST study, was provided. This amendment also included an updated Investigator Brochure for Carfilzomib (V17 dated 13/10/2016) along with the comparative table of changes to the IB from the previous version (V16 dated 16/01/2016). The Chief Investigator confirmed this did not affect the safety of the trial. The trial continued to use the Investigator Brochure as the Reference Safety Information (V17) and did not adopt the Carfilzomib Summary of Product Characteristics. Also included in this amendment was an update to the applicant contact details listed in sections C1-4 and G5 of Annex 1.
02 January 2018	This amendment was concerned with changing the PI at one of the sites, Norwich Hospital.

03 April 2018	An earlier substantial amendment was rejected by the MHRA on the following grounds: "- Exclusion criterion #22 and the information on hepatitis B reactivation in section 9.3.3 have been removed with no justification and without being declared. This is not acceptable and these must be reinstated into protocol version 3.0." This occurred due to an error at the CTRU, where an incorrect previous version of the protocol was used to form version 3.0. Attached to the current submission were the following documents: Protocol v3.0, 24th January 2018 Protocol v3.0 24th January 2018_tracked changes Patient Information Sheet v4.0 24th January 2018 Patient Information Sheet v4.0 24th January 2018_tracked changes IB for Carfilzomib v18.0 26th September 2017 IB v18.0 Summary of changes 26th September 2017 Dexamethasone SmPC 26th January 2018 Dexamethasone SmPC Changes 29th January 2018 Thalidomide SmPC 16th February 2017 Thalidomide SmPC changes 24th January 2018 Substantial amendment form A form which highlights a summary of the changes made to the protocol and PIS. Revised PDF copy of the Clinical Trial Agreement with changes highlighted, and also a revised XML file These amendments didn't affect the risk benefit of this trial.
06 June 2018	This amendment was concerned with the addition of University College London Hospitals as site.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported