



## Clinical trial results:

### A Pilot study of Response to Velcade combination chemotherapy in AL amyloidosis (REVEAL)

#### Summary

EudraCT number	2009-014906-33
Trial protocol	GB
Global end of trial date	18 December 2014

#### Results information

Result version number	v1 (current)
This version publication date	09 April 2017
First version publication date	09 April 2017

#### Trial information

##### Trial identification

Sponsor protocol code	UCL/08/0254
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##### Additional study identifiers

ISRCTN number	ISRCTN33283585
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	University College London
Sponsor organisation address	Joint Research Office, Gower Street, London, United Kingdom, WC1E 6BT
Public contact	REVEAL Trial Coordinator, CR UK & UCL Cancer Trials Centre , ctc.sponsor@ucl.ac.uk
Scientific contact	REVEAL Trial Coordinator, CR UK & UCL Cancer Trials Centre , 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:



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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	21 January 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	18 December 2014
Was the trial ended prematurely?	Yes

Notes:

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**General information about the trial**

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Main objective of the trial:

To assess the efficacy, safety and tolerability of two bortezomib-based combination chemotherapy regimens:

VD (bortezomib [Velcade], and dexamethasone) and CVD (cyclophosphamide, bortezomib [Velcade] and dexamethasone) in a randomized parallel phase II design in patients with AL amyloidosis who have Mayo stage II or III disease.

Protection of trial subjects:

Due to the potential effect of the trial treatment on pregnancy and lactation, and effect of doxorubicin on exposed sperm, the trial subjects had consented to use a reliable and acceptable form of contraception during the trial and for at least 6 months after the last trial treatment. All women of childbearing potential at risk of becoming pregnant had to undergo pregnancy tests during baseline investigations and prior to start of each cycle.

Since the trial population were patients with cardiac amyloidosis, a 24 hour Holter monitor was used to monitor heart rate and rhythm. Trial subjects who experienced related non-haematological toxicity had their next dose of the drug withheld or delayed start of next cycle, those who experienced grade 4 neutropenia or febrile neutropenia were considered for G-CSF. The trial treatment were to be discontinued if already withheld and the AE did not resolve as expected. For adverse events attributable to Bortezomib, other than peripheral neuropathy, re-start of the treatment was to be at a reduced dose after resolution. The trial also incorporated several dose adjustments for renal and hepatic insufficiency. Since fluid retention is a common side effect of Dexamethasone in patients with amyloidosis, optimisation and close monitoring of fluid balance or dose adjustment of the drug was advised.

Trial subjects who experienced generalised oedema, greater than grade 3 local reactions or painful local reactions were allowed intravenous administration of bortezomib until resolution of the reaction.

Trial subjects had regular clinic visits during and after treatment where they were assessed for toxicity and monitored for adverse events. If these occurred out of clinic hours, all trial subjects were given patient cards with contact details of the local haematology team that they could access at any time for advice.

All trial subjects received prophylaxis during treatment and until a specified time after as applicable.

Background therapy:

- Oral acyclovir 200 mg three times daily with dose modified according to renal function or appropriate alternative.
- Oral Lansoprazole 15 mg once daily or Omeprazole 20mg once daily or appropriate alternative
- Oral Fluconazole 50mg once daily (unless contraindicated due to abnormal liver function tests or allergy)
- Oral Co-trimoxazole 480 mg twice daily given three times weekly (unless contraindicated).

Evidence for comparator: -



Actual start date of recruitment	12 July 2007
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

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### Population of trial subjects

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#### Subjects enrolled per country

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Country: Number of subjects enrolled	United Kingdom: 7
Worldwide total number of subjects	7
EEA total number of subjects	7

Notes:

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#### Subjects enrolled per age group

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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)	5
From 65 to 84 years	2
85 years and over	0



## Subject disposition

### Recruitment

Recruitment details:

The 7 trial subjects were recruited between 15/03/2012 - 26/07/2013 from 2 Trial Sites.

### Pre-assignment

Screening details:

Patients aged at least 18 years presenting with systemic AL amyloidosis with measurable clonal disease and of Mayo stage II or III were screened for eligibility at the Trial site. The participating investigators kept screening logs of all patients screened for eligibility who were not registered in the trial due to ineligibility.

### 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
<b>Arm title</b>	PAD Regimen

Arm description:

Bortezomib, Doxorubicin & Dexamethasone

Arm type	Experimental
Investigational medicinal product name	Bortezomib
Investigational medicinal product code	L01XX32
Other name	Velcade
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Initially, bortezomib was given twice weekly in combination with Doxorubicin and Dexamethasone (PAD) at a dose of 1mg/m<sup>2</sup> intravenously on days 1, 4, 8 and 11 of each 21-day cycle for a minimum of 3 cycles to a maximum of 6 cycles. This was given with doxorubicin at 18mg/m<sup>2</sup> i.v. on days 1 & 8 and dexamethasone at 20mg PO on days 1, 4, 8 and 11.

Following a protocol amendment, route of administration for bortezomib was changed to subcutaneous and day 8 of doxorubicin removed from the schedule.

<b>Arm title</b>	VD Regimen
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Arm description:

Bortezomib with Dexamethasone

Arm type	Experimental
Investigational medicinal product name	Bortezomib
Investigational medicinal product code	L01XX32
Other name	Velcade
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

After a review of the safety data by the IDMC, the trial protocol was amended to remove doxorubicin from the combination regimen. Patients from this point onward were treated on bortezomib and dexamethasone.

Dosage and administration of bortezomib was changed to from twice weekly to weekly in combination with Dexamethasone only (VD) at a dose of 1.3mg/m<sup>2</sup> s.c. on days 1, 8, 15 and 22 of each 35-day



cycle for a minimum of 3 cycles to a maximum of 6 cycles.

Dexamethasone was given 20mg PO on days 1, 8, 15 and 22

<b>Arm title</b>	CVD Regimen
Arm description: Cyclophosphamide, Bortezomib and Dexamethasone	
Arm type	Experimental
Investigational medicinal product name	Bortezomib
Investigational medicinal product code	L01XX32
Other name	Velcade
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Initially, bortezomib was given twice weekly with the combination of cyclophosphamide and dexamethasone (CVD) at a dose of  $1\text{mg}/\text{m}^2$  on days 1, 4, 8, 11 and 15 of each 21-day cycle for a minimum of 3 cycles to a maximum of 6 cycles.

After a protocol amendment, dosage and administration was changed to weekly in at a dose of  $1.3\text{mg}/\text{m}^2$  on days 1, 8, 15 and 22 of each 35-day cycle for a minimum of 3 cycles to a maximum of 6 cycles.

Cyclophosphamide was given  $350\text{mg}/\text{m}^2$  (max 500mg) PO on days 1 and 15

Dexamethasone 20mg PO on days 1 - 4

<b>Number of subjects in period 1</b>	PAD Regimen	VD Regimen	CVD Regimen
Started	3	1	3
Completed	2	1	1
Not completed	1	0	2
Adverse event, serious fatal	1	-	2



## Baseline characteristics

### Reporting groups

Reporting group title	PAD Regimen
Reporting group description: Bortezomib, Doxorubicin & Dexamethasone	
Reporting group title	VD Regimen
Reporting group description: Bortezomib with Dexamethasone	
Reporting group title	CVD Regimen
Reporting group description: Cyclophosphamide, Bortezomib and Dexamethasone	

Reporting group values	PAD Regimen	VD Regimen	CVD Regimen
Number of subjects	3	1	3
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	2	0	3
From 65-84 years	1	1	0
85 years and over	0	0	0
Age continuous			
Units: years			
median	57	68	48
full range (min-max)	57 to 65	68 to 68	35 to 59
Gender categorical			
Units: Subjects			
Female	1	0	1
Male	2	1	2
ECOG performance status			
Grade 0 - Fully Active - Able to carry out all normal activity without restriction			
Grade 1 - Work Able - Restricted in physically strenuous activity; ambulatory, can do light work			
Grade 2 - Not Work Able - Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours			
Grade 3 - Limited Self Care - Capable of only limited self-care; confined to bed or chair for more than 50% of waking hours			
Grade 4 - Disabled - Completely disabled; cannot carry out any self-care; totally confined to bed or chair			
Units: Subjects			
Fully Active	1	0	0
Work Able	2	1	1
Not Work Able	0	0	1
Limited Self Care	0	0	1
Disabled	0	0	0
NYHA Class			



<b>NYHA Heart Failure Class</b> I - Patients with no limitation of activities; they suffer no symptoms from ordinary activities. II - Patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion. III - Patients with marked limitation of activity; they are comfortable only at rest. IV - Patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.			
Units: Subjects			
Class I	2	0	0
Class II	1	1	2
Class III	0	0	1
Class IV	0	0	0
Mayo Stage			
Stage I: Both NT-proBNP and cardiac troponin-T normal defined as NT-proBNP ≤36 pMol/L and cardiac troponin T ≤0.03 ng/ml (or cardiac high sensitivity troponin T ≤ 0.05 µg/L) Stage II: Either one of NT-proBNP or cardiac troponin T abnormal defined as: NT-proBNP>36 pMol/L or cardiac troponin T >0.03 ng/ml (or cardiac high sensitivity troponin T >0.05 µg/L) Stage III: Both NT-proBNP and cardiac troponin T abnormal defined as: NT-proBNP >36 pMol/L and cardiac troponin T >0.03 ng/ml (or cardiac high sensitivity troponin T >0.05 µg/L)  As published by Dispenzieri et al 2004.			
Units: Subjects			
Stage I	0	0	0
Stage II	2	1	0
Stage III	1	0	3
Organ Involvement Site			
Amyloid-related organ site			
Units: Subjects			
Heart	1	0	1
Heart & Kidney	1	0	2
Heart & Other Organs	1	0	0
Kidney	0	1	0

<b>Reporting group values</b>	Total		
Number of subjects	7		
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)	5		
From 65-84 years	2		
85 years and over	0		
Age continuous			
Units: years			
median			
full range (min-max)	-		
Gender categorical			
Units: Subjects			
Female	2		
Male	5		



ECOG performance status			
Grade 0 - Fully Active - Able to carry out all normal activity without restriction Grade 1 - Work Able - Restricted in physically strenuous activity; ambulatory, can do light work Grade 2 - Not Work Able - Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours Grade 3 - Limited Self Care - Capable of only limited self-care; confined to bed or chair for more than 50% of waking hours Grade 4 - Disabled - Completely disabled; cannot carry out any self-care; totally confined to bed or chair			
Units: Subjects			
Fully Active	1		
Work Able	4		
Not Work Able	1		
Limited Self Care	1		
Disabled	0		
NYHA Class			
NYHA Heart Failure Class I - Patients with no limitation of activities; they suffer no symptoms from ordinary activities. II - Patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion. III - Patients with marked limitation of activity; they are comfortable only at rest. IV - Patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.			
Units: Subjects			
Class I	2		
Class II	4		
Class III	1		
Class IV	0		
Mayo Stage			
Stage I: Both NT-proBNP and cardiac troponin-T normal defined as NT-proBNP $\leq 36$ pMol/L and cardiac troponin T $\leq 0.03$ ng/ml (or cardiac high sensitivity troponin T $\leq 0.05$ $\mu$ g/L) Stage II: Either one of NT-proBNP or cardiac troponin T abnormal defined as: NT-proBNP $> 36$ pMol/L or cardiac troponin T $> 0.03$ ng/ml (or cardiac high sensitivity troponin T $> 0.05$ $\mu$ g/L) Stage III: Both NT-proBNP and cardiac troponin T abnormal defined as: NT-proBNP $> 36$ pMol/L and cardiac troponin T $> 0.03$ ng/ml (or cardiac high sensitivity troponin T $> 0.05$ $\mu$ g/L)  As published by Dispenzieri et al 2004.			
Units: Subjects			
Stage I	0		
Stage II	3		
Stage III	4		
Organ Involvement Site			
Amyloid-related organ site			
Units: Subjects			
Heart	2		
Heart & Kidney	3		
Heart & Other Organs	1		
Kidney	1		



## End points

### End points reporting groups

Reporting group title	PAD Regimen
Reporting group description: Bortezomib, Doxorubicin & Dexamethasone	
Reporting group title	VD Regimen
Reporting group description: Bortezomib with Dexamethasone	
Reporting group title	CVD Regimen
Reporting group description: Cyclophosphamide, Bortezomib and Dexamethasone	

### Primary: Clonal response of the underlying plasma cell dyscrasia

End point title	Clonal response of the underlying plasma cell dyscrasia <sup>[1]</sup>
End point description: No statistical analyses was done due to small number of Trial subjects	
End point type	Primary
End point timeframe: Response was assessed at the end of 3 cycles of chemotherapy	

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 trial was prematurely terminated, thus a small number of trial subjects was recruited. No statistical analysis for the primary endpoint could be done due to the sample size.

End point values	PAD Regimen	VD Regimen	CVD Regimen	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	1	3	
Units: Trial Subjects	1	1	1	

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Trial subjects alive at 12 months

End point title	Number of Trial subjects alive at 12 months
End point description: Note: No statistical analyses have been specified for the endpoint.	
Due to premature closure of trial, only a few trial subjects were recruited, therefore formal statistical analyses could not be carried out	
End point type	Secondary
End point timeframe: From date of first randomisation to 12 months post first randomisation	



<b>End point values</b>	PAD Regimen	VD Regimen	CVD Regimen	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	1	3	
Units: percentage	1	1	1	

<b>Attachments (see zip file)</b>	Overall Survival/2009_014906_33_Reveal_Overall Survival.pdf
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### Statistical analyses

No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All adverse events (including serious) that occurred between informed consent and 30 days post last trial treatment administration (or after this date if thought to be related to the trial treatment)

Adverse event reporting additional description:

Trial subjects were assessed for adverse events prior the start of each treatment cycle. All adverse events were recorded in the patient notes and the trial CRFs. Those meeting the definition of a Serious Adverse Event were also reported using the trial specific SAE Reporting template.

Assessment type	Systematic
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### Dictionary used

Dictionary name	NCI - CTCAE
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Dictionary version	4.03
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### Reporting groups

Reporting group title	PAD Regimen
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Reporting group description:

Bortezomib, Doxorubicin & Dexamethasone

Reporting group title	VD Regimen
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Reporting group description:

Bortezomib with Dexamethasone

Reporting group title	CVD Regimen
-----------------------	-------------

Reporting group description:

Cyclophosphamide, Bortezomib and Dexamethasone

Serious adverse events	PAD Regimen	VD Regimen	CVD Regimen
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	1 / 1 (100.00%)	3 / 3 (100.00%)
number of deaths (all causes)	2	0	2
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	0 / 3 (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
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	2 / 3 (66.67%)	0 / 1 (0.00%)	2 / 3 (66.67%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 2
Respiratory, thoracic and mediastinal disorders			



Epistaxis			
subjects affected / exposed	0 / 3 (0.00%)	1 / 1 (100.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Delusion			
subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychosis			
subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	0 / 3 (0.00%)	0 / 1 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	0 / 3 (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
Lung infection			
subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	0 / 3 (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	PAD Regimen	VD Regimen	CVD Regimen
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 3 (66.67%)	1 / 1 (100.00%)	1 / 3 (33.33%)



Nervous system disorders	Dizziness			
	subjects affected / exposed	0 / 3 (0.00%)	0 / 1 (0.00%)	1 / 3 (33.33%)
	occurrences (all)	0	0	1
	Lethargy			
	subjects affected / exposed	0 / 3 (0.00%)	0 / 1 (0.00%)	1 / 3 (33.33%)
	occurrences (all)	0	0	1
	Syncope			
	subjects affected / exposed	0 / 3 (0.00%)	0 / 1 (0.00%)	1 / 3 (33.33%)
	occurrences (all)	0	0	1
Blood and lymphatic system disorders	Anaemia			
	subjects affected / exposed	0 / 3 (0.00%)	0 / 1 (0.00%)	1 / 3 (33.33%)
	occurrences (all)	0	0	1
General disorders and administration site conditions	Localised oedema			
	subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	0 / 3 (0.00%)
	occurrences (all)	1	0	0
	Fatigue			
	subjects affected / exposed	2 / 3 (66.67%)	1 / 1 (100.00%)	1 / 3 (33.33%)
	occurrences (all)	2	1	1
	Haemorrhage			
	subjects affected / exposed	0 / 3 (0.00%)	1 / 1 (100.00%)	0 / 3 (0.00%)
	occurrences (all)	0	1	0
	Pain			
	subjects affected / exposed	0 / 3 (0.00%)	1 / 1 (100.00%)	1 / 3 (33.33%)
	occurrences (all)	0	1	1
Gastrointestinal disorders	Constipation			
	subjects affected / exposed	0 / 3 (0.00%)	0 / 1 (0.00%)	1 / 3 (33.33%)
	occurrences (all)	0	0	1
	Diarrhoea			
	subjects affected / exposed	0 / 3 (0.00%)	1 / 1 (100.00%)	0 / 3 (0.00%)
	occurrences (all)	0	1	0
Oral dysaesthesia				



subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 1 (100.00%) 1	0 / 3 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 1 (0.00%) 0	0 / 3 (0.00%) 0
Hiccups subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 1 (100.00%) 1	0 / 3 (0.00%) 0
Skin and subcutaneous tissue disorders Dry skin subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 1 (100.00%) 1	0 / 3 (0.00%) 0
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 1 (0.00%) 0	0 / 3 (0.00%) 0
Musculoskeletal and connective tissue disorders Other - Cramps in ankle and leg subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 1 (100.00%) 1	0 / 3 (0.00%) 0
Other - leg Cramp subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 1 (0.00%) 0	1 / 3 (33.33%) 1
Other - Night cramps subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 1 (100.00%) 1	0 / 3 (0.00%) 0
Other - spasm in left hand subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 1 (100.00%) 1	0 / 3 (0.00%) 0
Infections and infestations infection with normal ANC subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 1 (0.00%) 0	0 / 3 (0.00%) 0



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 December 2011	<ul style="list-style-type: none"><li>• The eligibility criteria was changed to include untreated Mayo Stage II and III patients with AL amyloidosis instead of pre-treated relapsed or refractory patients.</li><li>• IV administration of bortezomib was replaced by subcutaneous administration as main route of administration. IV administration was allowed if a patient had conditions which in the investigator's assessment would contraindicate use of bortezomib subcutaneously.</li></ul>
01 June 2012	<p>An urgent safety measure was implemented on 01/06/2012, recruitment was suspended with immediate effect. A higher than expected rate of sudden cardiac deaths among the first few patients entered into the trial was seen had been reported thus requiring a necessary review of the safety data by the Independent Data Monitoring Committee before further patients could be recruited.</p> <p>Sites were informed that they were not to approach further patients about participating in the trial until further notice.</p>
29 October 2012	<p>A substantial amendment was submitted for approval for the re-start of the trial following the Urgent Safety Measure and also to implement changes made to the trial schedule and relevant trial documentation.</p> <ul style="list-style-type: none"><li>• Removal of doxorubicin from the PAD regimen</li><li>• Increase of cycle days from 21 to 35</li><li>• Bortezomib dosage changed from twice weekly to weekly dose.</li></ul>
24 January 2013	<p>This substantial amendment was sent to the REC only.</p> <p>Change of Principal Investigator:</p> <ul style="list-style-type: none"><li>- Dr Stephen Hawkins has replaced Dr Patrick Chu at Royal Liverpool University Hospitals NHS Trust</li></ul> <p>Addition of Research Site:</p> <p>Central Manchester University Hospitals NHS FT, Manchester Royal Infirmary;</p> <p>Principal Investigator: Dr Simon Gibbs</p>
08 April 2013	<p>This substantial amendment was sent to the REC only.</p> <p>The Patient Information Sheet and GP Letter were updated to correct the information given regarding the number of visits to be made by the trial subjects to the National Amyloidosis Centre.</p>
29 October 2014	<p>This substantial amendment was sent to the REC only.</p> <p>The premature closure of 2 sites was requested, as they had notified us they would no longer be able to take part in the clinical trial.</p>

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
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01 June 2012	<p>An urgent safety measure was implemented on 01/06/2012, recruitment was suspended with immediate effect. A higher than expected rate of sudden cardiac deaths among the first few patients entered into the trial was seen had been reported thus requiring a necessary review of the safety data by the Independent Data Monitoring Committee before further patients could be recruited.</p> <p>Sites were informed that they were not to approach further patients about participating in the trial until further notice.</p>	15 February 2013
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Notes:

## Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

- Serious and non-serious AEs are listed under non-serious AEs
- Non-serious AEs: 'occurrences all number' can't be provided as only highest grade experienced by patients are collected on CRFs; subjects affected number is entered instead.

Notes: