Clinical trial results:
Phase II study of Bortezomib, Adriamycin and Dexamethasone (PAD) therapy for previously untreated patients with multiple myeloma: Impact of minimal residual disease (MRD) in patients with deferred ASCT (PADIMAC)

Summary

EudraCT number	2010-021598-35
Trial protocol	GB
Global end of trial date	13 November 2019

Results information

Result version number	v1 (current)
This version publication date	03 May 2021
First version publication date	03 May 2021

Trial information

Trial identification

Sponsor protocol code	UCL/08/0255

Additional study identifiers

ISRCTN number	ISRCTN03381785
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Funder reference: LRF/10018, REC reference : 10/H0502/58

Notes:

Sponsors

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

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 May 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

PADIMAC is a phase II study designed as a single arm study to evaluate the safety of a no treatment option for patients achieving CR/VGPR post induction therapy on the PAD regimen and not proceeding to ACST.
The main objective of the study is to provide a reliable estimate of the 2-year progression-free survival (PFS) for patients who, having achieved CR/VGPR following PAD therapy (measured following peripheral blood stem cell harvest, PBSCH), do not receive any further treatment until clinical indication of relapse. This is addressed separately for patients who are minimal residual disease positive (MRD+), and those who are MRD negative (MRD-), at end of induction therapy.

Protection of trial subjects:

Pregnancy testing prior to each treatment cycle was mandated for all women of child bearing potential, due to the unknown risk from bortezomib exposure to human embryo /foetus, crossing of dexamethasone through the placenta causing possible foetal development abnormalities and possible teratogenicity of doxorubicin. All patients had to consent to trial acceptable methods of contraception during the study and for six months post trial treatment. Due to the possible effect of doxorubicin on male fertility, for safety reasons, men wanting babies were advised on sperm cryopreservation prior to trial treatment.

Patients who did not achieve at least a PR following trial treatment, immediately went on to receive salvage treatment. Patients who were assigned to no further treatment, following trial treatment and a negative MRD result, were offered off-trial ASCT on relapse. Cardiac function assessment was done at the end of trial treatment, due to possible cardiotoxicity from doxorubicin.

Local supportive care protocols including antiemetic schedules, mesna, thromboprophylaxis (to prevent tumour lysis), transfusion support, mouthcare and prophylactic antimicrobial therapy were followed as required.

Prior to each trial treatment dose, patients were evaluated for possible toxicities that might have occurred from the previous dose. For each of the trial drugs, dose modifications were put in place for specific haematological and non-haematological toxicities. Treatment delays were also allowed for toxicities that were not related to any of the trial drugs.

Background therapy:

Patients who achieved at least a partial response (PR) following the trial treatment received PBSC Mobilisation before peripheral blood stem cell harvest (PBSCH):
Cyclophosphamide, iv infusion in 500 ml NaCl 0.9%, 1.5-3 g/m^2
G-CSF, subcutaneous, 5-10 mcg/kg/day or 150 mcg/m^2/day

Patients who achieved a partial response (PR) with adequate PBSCH, received high dose melphalan with autologous stem cell rescue (ASCT):
NaCl 0.9% + 20 mmol KCl, 1 litre/hour
Furosemide, 20 to 40 mg, IV stat
Dexamethasone, 8 mg, IV stat
Granisetron, 3 mg, IV stat
Melphalan, 200 mg/m^2, short infusion (as per local protocol) in 100 ml NaCl 0.9%
NaCl 0.9%, 1 litre over 2 hours + KCl 20 mmol to maintain urine output of at least 500 ml/hr
NaCl 0.9% + KCl 1 litre four hourly x 1
NaCl 0.9% + KCl 1 litre six hourly x 3

Evidence for comparator: -	
Actual start date of recruitment	01 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: 153
Worldwide total number of subjects	153
EEA total number of subjects	0

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)	129
From 65 to 84 years	24
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

14 UK sites were opened to participate in the trial over a period of 2 years (09/03/2011 to 13/03/2013). Of these, only 13 recruited patients into the trial.
A total of 153 patients were recruited over 2 years and 9 months (01/04/2011 - 14/01/2014), a planned increase from the initial 120 target.

Pre-assignment

Screening details:

Patients aged ≥18 years with previously untreated symptomatic myeloma were screened. They had to have measurable disease, suitable for high dose therapy and ASCT, adequate full blood count, renal, cardiac, pulmonary and hepatobiliary functions. Patients with ≥Gr2 peripheral neuropathy/neuropathic pain were excluded. Screening logs were maintained.

Period 1

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

Arms

Arm title	PAD Regimen

Arm description:

Bortezomib (Velcade), Doxorubicin and Dexamethasone

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

Dosage and administration details:

At the start of the trial, bortezomib was given twice weekly in combination with Doxorubicin and Dexamethasone (PAD) at a dose of 1.3mg/m^2 as a bolus IV injection on days 1, 4, 8 and 11 of each 21-day cycle for a minimum of 4 cycles to a maximum of 6 cycles. It was given with doxorubicin on days 1 & 4 and with dexamethasone on days 1 & 4 for every cycle and days 8 & 11 for the first cycle only. Dose was calculated on D1 of each cycle and same dose was administered through out the days of that cycle. If a notable change in weight occurred within a cycle, as determined by an unscheduled weight assessment, dose was to be recalculated at that time.

Following protocol amendments, bortezomib administration was changed to subcutaneous (2011) and then to either subcutaneous or intravenous routes (2014) using the same schedule. The preferred route of administration was subcutaneous, but IV injection was allowed only if a patient experienced ≥Gr2 SC injection site reactions.

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	L01DB01
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

9mg/m^2 /day as continuous IV infusion or by IV bolus injection, on days 1 - 4 of each 21 day cycle (minimum 4, maximum 6).
Doxorubicin was given with bortezomib on days 1 & 4, and with dexamethasone on days 1 - 4. Dose was calculated on D1 of each cycle and same dose was administered through out the days of that cycle.

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	A01AC02, C05AA09
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

40 mg/day on days 1 - 4 of each 21 day cycle (minimum of 4 and a maximum of 6). For the first cycle only, it was also administered on days 8 - 11 and days 15 - 18.
It was given, in every cycle, with doxorubicin on days 1 - 4 and with bortezomib on days 1 & 4 (and days 8 & 11 for the first cycle only).

Number of subjects in period 1	PAD Regimen
Started	153
Completed	139
Not completed	14
Patient decision	1
Physician decision	5
Adverse event, non-fatal	4
Lack of efficacy	4

Baseline characteristics

Reporting groups

Reporting group title	Main trial (overall period)

Reporting group description: -

Reporting group values	Main trial (overall period)	Total	
Number of subjects	153	153	
Age categorical Units: Subjects			
Adults (18-64 years)	129	129	
From 65-84 years	24	24	
85 years and over	0	0	
Age continuous			
Dates of birth were collected on the case report forms, and age calculated from date registered and birth dates.			
Units: years			
median	55		
full range (min-max)	28 to 71	-	
Gender categorical Units: Subjects			
Female	55	55	
Male	98	98	
ECOG Performance Status			
0 - Fully active, able to carry on all pre-disease performance without restriction 1 - Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work 2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours 3 - Capable of only limited self-care, confined to bed or chair more than 50% of waking hours 4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair 5 - Dead			
Units: Subjects			
Grade 0	55	55	
Grade 1	73	73	
Grade 2	15	15	
Grade 3	9	9	
Missing	1	1	
International Staging System (ISS) for Multiple Myeloma			
I - Serum β2-microglogulin <3.5mg/L; serum albumin >3.5g/dL II - Serum β2-microglogulin <3.5mg/L but serum albumin < 3.5g/dL OR Serum β2-microglogulin 3.5 to < 5.5mg/L irrespective of serum albumin level III - Serum ß2-microglobulin 5.5 mg/L			
Units: Subjects			
Stage 1	51	51	
Stage 2	67	67	
Stage 3	34	34	
Missing	1	1	
Paraprotein Isotype Units: Subjects			
IgG	111	111	

IgA	26	26	
LC (Light Chain)	16	16	
Cytogenetic Risk by FISH Units: Subjects			
Standard risk	113	113	
Adverse risk	20	20	
Missing	20	20	

End points

End points reporting groups

Reporting group title	PAD Regimen
Reporting group description:	
Bortezomib (Velcade), Doxorubicin and Dexamethasone	

Primary: 2-year PFS by MRD status within the VGPR-W&W group

End point title	2-year PFS by MRD status within the VGPR-W&W group[1]
End point description:	
2-year progression free survival (PFS) for patients post PBSCH, who receive no further treatment after achieving a major response to induction therapy with PAD.	
End point type	Primary
End point timeframe:	
Time from date of PBSCH to date of the first progression/relapse or date of death from all causes whichever occurs first estimated at 2 years post-PBSCH.	

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: Primary analyses are descriptive, with simple estimates and 95% confidence intervals. Exploratory comparison by MRD status at day 100: Cox regression HR=0.74 (95% CI: 0.40-1.37, p=0. 33)

End point values	PAD Regimen			
Subject group type	Reporting group			
Number of subjects analysed	50[2]			
Units: percent				
number (confidence interval 95%)				
MRD -ve	55.6 (30.5 to 74.8)			
MRD +ve	31.3 (16.4 to 47.3)			

Notes:

[2] - Number here is the 2-year rate

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response (OR) to PAD induction therapy

End point title	Overall Response (OR) to PAD induction therapy
End point description:	
Disease response was measured by serum and urinary paraprotein, with Complete Response (CR), Very Good partial Response (VGPR), Partial Response (PR), Stable Disease (SD) and Progressive Disease (PD) defined as per the International response criteria (Durie et al, 2006). Patients achieving CR and VGPR were categorised as the ≥VGPR group.	
End point type	Secondary
End point timeframe:	
Time from start of PAD therapy until post PBSCH	

End point values	PAD Regimen			
Subject group type	Reporting group			
Number of subjects analysed	153[3]			
Units: Subjects				
<PR post PAD	27			
≥VGPR post PBSCH	63			
PR post PBSCH	44			
PD post PBSCH	2			
≥post-PAD no harvest	17			

Notes:

[3] - 36/44 PR post-PBSCH had ASCT
OR rate post induction = 82.4%(126/153) with 63(41.2%) achieving ≥VGPR

Statistical analyses

No statistical analyses for this end point

Secondary: MRD status post PBSCH

End point title	MRD status post PBSCH

End point description:

MRD was assessed by Multiparameter Flow Cytometry (MPF) of bone marrow samples from patients after PBSCH

End point type	Secondary

End point timeframe:

MRD status was assessed post stem cell harvesting (PBSCH)

End point values	PAD Regimen			
Subject group type	Reporting group			
Number of subjects analysed	153[4]			
Units: Subjects				
MRD +ve	65			
MRD -ve	22			
Missing	66			

Notes:

[4] - MRD -ve (25.3%)
MRD +ve (74.7%)

Statistical analyses

No statistical analyses for this end point

Secondary: MRD status at D100 post-ASCT for PR-ASCT group

End point title	MRD status at D100 post-ASCT for PR-ASCT group

End point description:

MRD was assessed by MPF of bone marrow samples from patients after stem cell harvesting, at 100

days post ASCT for PR patients

End point type	Secondary

End point timeframe:

MRD assessed at 100 days post ASCT

End point values	PAD Regimen			
Subject group type	Reporting group			
Number of subjects analysed	36[5]			
Units: Subjects				
MRD +ve	20			
MRD -ve	7			
Missing	9			

Notes:

[5] - 20 (74.1%) and 7 (25.9%)

Statistical analyses

No statistical analyses for this end point

Secondary: MRD status at D100 post-PBSCH for VGPR-W&W group

End point title	MRD status at D100 post-PBSCH for VGPR-W&W group

End point description:

MRD was assessed by MPF of bone marrow samples from patients at 100 days post-PBSCH for ≥VGPR patients. These are the patients that received no further treatment until relapse (VGPR-W&W)

End point type	Secondary

End point timeframe:

MRD assessment at 100 days post-PBSCH

End point values	PAD Regimen			
Subject group type	Reporting group			
Number of subjects analysed	63[6]			
Units: Subjects				
MRD +ve	32			
MRD -ve	18			
Missing	13			

Notes:

[6] - 32 (64.0%) and 18 (36.0%)

Statistical analyses

No statistical analyses for this end point

Secondary: PFS post-PBSCH for PR-ASCT group

End point title	PFS post-PBSCH for PR-ASCT group

End point description:

Progression free survival (PFS) of patients proceeding to ASCT (PR-ASCT), following PBSCH

End point type	Secondary

End point timeframe:

Time from date of Peripheral Blood Stem Cell Harvest (PBSCH), following PAD therapy, to date of the first progression/relapse or date of death from all causes whichever occurs first

End point values	PAD Regimen			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: Months				
median (confidence interval 95%)				
PR-ASCT 2-year PFS	19.6 (17.0 to 22.8) 33.3 (18.8 to 48.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: 2-year PFS2 rate post-PBSCH

End point title	2-year PFS2 rate post-PBSCH

End point description:

Patients were followed up from PBSCH until second disease relapse or death.

End point type	Secondary

End point timeframe:

2 years from date of PBSCH to the second relapse or death

End point values	PAD Regimen			
Subject group type	Reporting group			
Number of subjects analysed	99[7]			
Units: Percentage				
number (confidence interval 95%)				
VGPR-W&W PR-ASCT	77.3 (64.7 to 85.9) 97.2 (81.9 to 99.6)			

Notes:

[7] - This includes the PR-ASCT and VGPR-W&W groups.

Number refers to the 2-year rate

Statistical analyses

No statistical analyses for this end point

Secondary: 2-year OS rate

End point title	2-year OS rate

End point description:

Overall survival (OS) rate was measured from date of PBSCH to death. The VGPR-W&W and PR-ASCT groups were combined and OS was calculated by MRD status at
D100 post PBSCH

End point type	Secondary

End point timeframe:

2 years from date of PBSCH to death event

End point values	PAD Regimen			
Subject group type	Reporting group			
Number of subjects analysed	99[8]			
Units: percent				
number (confidence interval 95%)				
VGPR-W&W	91.9 (81.6 to 96.5)			
PR-ASCT	100 (90.3 to 100)			

Notes:

[8] - Number refers to the 2-year rate

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 occur between first administration of trial treatment (PAD) and 30 days post last trial treatment (PAD) 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 (AEs) prior the start of each PAD cycle. All AEs were recorded in the patient notes and the trial CRFs. Those meeting the definition of Serious, excluding exempted events, were to be reported using the trial specific SAE Reporting template within 24 hours of observing or learning of the event.

Assessment type	Systematic

Dictionary used

Dictionary name	NCI - CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	PAD therapy

Reporting group description:

Bortezomib, doxorubicin and dexamethasone

Serious adverse events	PAD therapy		
Total subjects affected by serious adverse events			
subjects affected / exposed	27 / 153 (17.65%)		
number of deaths (all causes)	43		
number of deaths resulting from adverse events	1		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 153 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 153 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Heart Failure			
subjects affected / exposed	1 / 153 (0.65%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			

Autonomic neuropathy				
subjects affected / exposed	1 / 153 (0.65%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral sensory neuropathy				
subjects affected / exposed	1 / 153 (0.65%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Dizziness				
subjects affected / exposed	1 / 153 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	1 / 153 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Fever				
subjects affected / exposed	1 / 153 (0.65%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Localised oedema				
subjects affected / exposed	1 / 153 (0.65%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	1 / 153 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Diarrhoea				
subjects affected / exposed	2 / 153 (1.31%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			

Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	1 / 153 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Hiccups			
subjects affected / exposed	1 / 153 (0.65%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 153 (0.65%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 153 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Avascular necrosis			
subjects affected / exposed	1 / 153 (0.65%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	1 / 153 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Lung Infection			
subjects affected / exposed	1 / 153 (0.65%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			

subjects affected / exposed	1 / 153 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatitis E				
subjects affected / exposed	1 / 153 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia	Additional description: Reported as pyrexia from chest infection			
subjects affected / exposed	1 / 153 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Dehydration				
subjects affected / exposed	1 / 153 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypercalcaemia				
subjects affected / exposed	1 / 153 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hyperglycaemia				
subjects affected / exposed	1 / 153 (0.65%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hyponatraemia				
subjects affected / exposed	2 / 153 (1.31%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			

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

Non-serious adverse events	PAD therapy		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	153 / 153 (100.00%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	9 / 153 (5.88%)		
occurrences (all)	9		
Thrombosis	Additional description: Reported as Thromboembolic event		
subjects affected / exposed	8 / 153 (5.23%)		
occurrences (all)	8		
General disorders and administration site conditions			
Localised oedema			
subjects affected / exposed	10 / 153 (6.54%)		
occurrences (all)	10		
Pain			
subjects affected / exposed	15 / 153 (9.80%)		
occurrences (all)	15		
Oedema	Additional description: Reported as 'Oedema - limbs'		
subjects affected / exposed	43 / 153 (28.10%)		
occurrences (all)	43		
Fatigue			
subjects affected / exposed	112 / 153 (73.20%)		
occurrences (all)	112		
Pyrexia	Additional description: Reported as 'Fever'		
subjects affected / exposed	22 / 153 (14.38%)		
occurrences (all)	22		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	12 / 153 (7.84%)		
occurrences (all)	12		
Cough			
subjects affected / exposed	19 / 153 (12.42%)		
occurrences (all)	19		
Psychiatric disorders			

Agitation			
subjects affected / exposed	8 / 153 (5.23%)		
occurrences (all)	8		
Insomnia			
subjects affected / exposed	44 / 153 (28.76%)		
occurrences (all)	44		
Investigations			
Neutrophil count decreased			
subjects affected / exposed	53 / 153 (34.64%)		
occurrences (all)	53		
Platelet count decreased			
subjects affected / exposed	35 / 153 (22.88%)		
occurrences (all)	35		
Alkaline phosphatase increased			
subjects affected / exposed	12 / 153 (7.84%)		
occurrences (all)	12		
Gamma-glutamyltransferase increased			
subjects affected / exposed	11 / 153 (7.19%)		
occurrences (all)	11		
Lymphocyte count decreased			
subjects affected / exposed	12 / 153 (7.84%)		
occurrences (all)	12		
White blood cell count decreased			
subjects affected / exposed	12 / 153 (7.84%)		
occurrences (all)	12		
Alanine aminotransferase increased			
subjects affected / exposed	21 / 153 (13.73%)		
occurrences (all)	21		
Nervous system disorders			
Peripheral sensory neuropathy			
subjects affected / exposed	105 / 153 (68.63%)		
occurrences (all)	105		
Dysgeusia			
subjects affected / exposed	14 / 153 (9.15%)		
occurrences (all)	14		
Headache			

subjects affected / exposed	15 / 153 (9.80%)		
occurrences (all)	15		
Paresthesia			
subjects affected / exposed	8 / 153 (5.23%)		
occurrences (all)	8		
Dizziness			
subjects affected / exposed	36 / 153 (23.53%)		
occurrences (all)	36		
Peripheral motor neuropathy	Additional description: Reported as 'Neuropathy (motor)'		
subjects affected / exposed	20 / 153 (13.07%)		
occurrences (all)	20		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	56 / 153 (36.60%)		
occurrences (all)	56		
Eye disorders			
blurred vision			
subjects affected / exposed	8 / 153 (5.23%)		
occurrences (all)	8		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	40 / 153 (26.14%)		
occurrences (all)	40		
Abdominal pain			
subjects affected / exposed	19 / 153 (12.42%)		
occurrences (all)	19		
Constipation			
subjects affected / exposed	83 / 153 (54.25%)		
occurrences (all)	83		
Diarrhoea			
subjects affected / exposed	51 / 153 (33.33%)		
occurrences (all)	51		
Nausea			
subjects affected / exposed	67 / 153 (43.79%)		
occurrences (all)	67		
Skin and subcutaneous tissue disorders			

Erythema multiforme			
subjects affected / exposed	8 / 153 (5.23%)		
occurrences (all)	8		
Alopecia			
subjects affected / exposed	27 / 153 (17.65%)		
occurrences (all)	27		
Rash			
subjects affected / exposed	40 / 153 (26.14%)		
occurrences (all)	40		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	53 / 153 (34.64%)		
occurrences (all)	53		
Bone pain			
subjects affected / exposed	8 / 153 (5.23%)		
occurrences (all)	8		
Pain in extremity	Additional description: Reported as pain in lower limbs		
subjects affected / exposed	12 / 153 (7.84%)		
occurrences (all)	12		
Pain - hip			
subjects affected / exposed	8 / 153 (5.23%)		
occurrences (all)	8		
Infections and infestations			
Infection			
subjects affected / exposed	10 / 153 (6.54%)		
occurrences (all)	10		
infection and infestation - other			
subjects affected / exposed	10 / 153 (6.54%)		
occurrences (all)	10		
Upper respiratory tract infection			
subjects affected / exposed	28 / 153 (18.30%)		
occurrences (all)	28		
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	8 / 153 (5.23%)		
occurrences (all)	8		

Hyperglycaemia			
subjects affected / exposed	8 / 153 (5.23%)		
occurrences (all)	8		
Hyponatraemia			
subjects affected / exposed	10 / 153 (6.54%)		
occurrences (all)	10		
Anorexia and bulimia syndrome	Additional description: Reported as 'Anorexia'		
subjects affected / exposed	20 / 153 (13.07%)		
occurrences (all)	20		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 July 2011	Protocol was amended to allow the following: - IV administration of bortezomib was replaced with subcutaneous administration - IV bolus injection administration of doxorubicin, administration of doxorubicin over 4 days (total dose 36/mg/m2) - inclusion criterion for Creatinine Clearance was changed from ≥ 30mL/min to ≥ 20mL/min - Serum free light chain essay was made mandatory post PBSCH and 100 days post PBSCH/ASCT Patient Information Sheet (PIS) was updated to include: - information on changed routes of administration for bortezomib and doxorubicin - additional details on effective contraception
29 November 2011	Urgent Safety Measure - There was an precautionary recall of the supplied bortezomib, Velcade, following a 'Dear Investigator' letter from the supplier. Due to GMP compliance issues identified at Ben Venue Laboratories, BVL, Ohio, USA, one of the manufacturing facilities for Velcade, there was a recall of batches manufactured at this site. Some of the clinical trial subcutaneous (SC) Velcade stock for the trial were affected and immediate action had to be taken as it was detrimental for patients not to receive treatment. The urgent measure taken was to allow patients to be treated subcutaneously using IV labelled trial supply, once it was confirmed by the manufacturer (Janssen) that the IV and SC formulations were the same. A site, where IV labelled supply was not available, was given the go ahead following confirmation from Janssen to administer the SC labelled supply from the affected batch to their patients. All sites were to revert to using new batches of unaffected sc labelled trial supply once received. Increased monitoring of adverse events at sites was advised. The plan of actions to be taken were discussed with the REC and MHRA before implementation.
30 November 2012	Protocol amendment: changes were made to protocol v2 - IV administration of bortezomib was allowed as an alternative route - Inclusion criteria states inclusion of patients with ECOG PS of 0-3. Patients with an ECOG performance score of >3 when this score is due to disease processes such as spinal cord compression, and who would otherwise have a score of ≤3, were included in the trial - exclusion of patients with active HIV, hepatitis B or C infection Detailed information on toxicity assessment, sample collection and other relevant information, were also included. The PIS was updated to include detailed explanation on side effects of bortezomib for both SC and IV routes, and other relevant updates made to the protocol.
29 August 2014	Target accrual number was increased from 120 to 153 Protocol was amended as follows: - Additional assessments and samples at relapse - RSI for subcutaneous bortezomib was changed from the Investigator's Brochure to the SPC

04 December 2014	Protocol was amended as follows: - Update to the trial endpoints and outcome measures: PFS2 (time from start of salvage treatment to 2nd relapse) and OS (overall survival) were added as secondary endpoints - Update to the outcome measures and assessment of the measures for the trial - Update to the long term follow-up schedule for the trial due to the addition of OS as a secondary endpoint - Update to the End of Trial definition

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.

Non-serious AEs: 'occurrences all number' can't be provided as only highest grade experienced by patients are collected on CRFs; number of subjects affected has been entered.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/33715154