Clinical trial results:
PHASE II STUDY OF BORTEZOMIB CONSOLIDATION AFTER HIGH DOSE THERAPY AND AUTOLOGOUS STEM CELL TRANSPLANTATION FOR MULTIPLE MYELOMA

Summary

EudraCT number	2008-006751-48
Trial protocol	GB
Global end of trial date	24 January 2019

Results information

Result version number	v1 (current)
This version publication date	28 March 2021
First version publication date	28 March 2021

Trial information

Trial identification

Sponsor protocol code	08/0170

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01517724
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	Public contact, CRUK and UCL Cancer Trials Centre, ctc.sponsor@ucl.ac.uk
Scientific contact	Scientific contact, CRUK and 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	20 September 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This was a phase II study of bortezomib consolidation after high dose therapy (HDT) and autologous stem cell transplant (ASCT) for multiple myeloma (MM).
The overall aim was to determine the effect of bortezomib consolidation on the outcome of ASCT in patients with MM, and to assess the effect of bortezomib consolidation on bone health, based on serum markers of osteoblast and osteoclast function.
The main objectives of the trial were to:
• determine the disease response at 6 and 12 months following autologous stem cell transplantation (ASCT) consolidated by bortezomib therapy. This tests the hypothesis that the intervention improves disease response following ASCT
• evaluate the safety, toxicity and tolerability of bortezomib as consolidation therapy following high dose melphalan (HDT) with Melphalan (200mg/m2) and ASCT.

Protection of trial subjects:

The risks to the safety of the trial subjects were those generally associated with chemotherapy. Patients were counselled about these side effects prior to starting treatment. They were monitored closely for toxicity and the protocol continuation criteria for therapy and dose modification prior to each cycle of the study drug. The protocol contained specific instructions for when study treatment should be withheld and when/if it was able to re-start. Those who developed side effects of moderate severity (Grade>2) had their dose of study medication reduced as per the protocol. As appropriate, patients were prescribed supportive medication to minimise any side effects. The protocol also had instructions on prohibited medications and those which could be used with caution.
In case side effects did occur 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.
Due to the potential effect of the trial treatment on pregnancy and lactation, the trial subjects had consented to use a highly effective method of birth control or a combination of two effective methods of contraception for 4 weeks before, during the trial and for at least 6 months after the last trial treatment administration. All women of childbearing potential had to undergo a pregnancy test prior to starting the study drug and at the start of every cycle. Breast feeding had to be discontinued during treatment with bortezomib

Background therapy:

All patients should receive oral acyclovir according to local hospital policy
The following medications and support therapies are examples of supportive care that were permitted:
- Laxatives
- Loperamide for the treatment of diarrhoea, starting after the first watery stool
- Antiemetic agents
- rh-EPO
- Antibiotics and antifungal treatments
- Omeprazole or lansoprazole

Evidence for comparator:

N/A

Actual start date of recruitment	02 December 2009
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: 40
Worldwide total number of subjects	40
EEA total number of subjects	40

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)	31
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The 40 trial subjects were recruited between 02/Dec/2009 and 27/Mar/2014 from two trial sites in the UK (Royal United Hospital and University College London (with whom the Royal Free Hospital merged during the trial).

Pre-assignment

Screening details:

Patients aged from 18 to 70 years with multiple myeloma who had not progressed 3-4 months after receiving high dose melphalan with ASCT

Period 1

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

Arms

Arm title	Bortezomib consolidaion

Arm description:

Bortezomib was given at 1.3 mg/m² by subcutaneous injection (or intravenously if the patient did not tolerate subcutaneous injection) on days 1, 8, 15 and 22 of each 4-week cycle. After 3 cycles and approximately (within 4 weeks of) 6 months post ASCT, patients underwent re-staging of their disease. Patients with progressive disease came off protocol.
All other patients continued treatment for a maximum of 8 cycles, as tolerated, and then stopped treatment.
Within 4 weeks of stopping treatment patients underwent re-staging of their disease

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

Dosage and administration details:

Bortezomib was given at 1.3mg/m2 by subcutaneous injection on days 1,8,15 and 22 of each 4 week cycle. Patients could receive up to 8 cycles of bortezomib.

Number of subjects in period 1	Bortezomib consolidaion
Started	40
Completed	29
Not completed	11
Consent withdrawn by subject	4
Disease progression	1
Adverse event, non-fatal	5
Withdrawn prior to treatment	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description:

INCLUSION CRITERIA:
MM patients who received high dose melphalan with ASCT 3-4 months before registration & have not progressed
Age 18 - 70 years
Life expectancy >6 months
Creatinine <400µmol/L
WHO performance status 0-2
Contraceptive precautions
EXCLUSION CRITERIA:
Received bortezomib previously or bisphosphonates since ASCT
On/systemic steroid therapy is planned
Disease progression at any stage
Past history of polio, cord compression or other neurological condition resulting in persisting neurological deficit ≥ grade 2
Severe hepatic impairment
Pregnant/lactating
Allergic reaction to compounds containing boron/mannitol
Severe cardiovascular disease
History of acute infiltrative pulmonary/pericardial disease
History of/has hypotension
Peripheral neuropathy ≥ grade 2 or neuropathic pain
Serious medical/psychiatric condition likely to interfere with participation
Received/used an experimental drug/medical device within 4 weeks before the planned start of treatment

Reporting group values	Overall Trial	Total	
Number of subjects	40	40	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	31	31	
From 65-84 years	9	9	
85 years and over	0	0	
Age continuous Units: years			
median	61		
full range (min-max)	43 to 69	-	
Gender categorical Units: Subjects			
Female	18	18	
Male	22	22	
Disease isotype Units: Subjects			
IgG	22	22	

IgA	9	9	
IgD	1	1	
Light chain only	7	7	
Non-secretory	1	1	
Induction regimen Units: Subjects			
Thalidomide-containing	35	35	
Idarubicin/dexamethasone	4	4	
Idarubicin\dexamethasone\cyclophosphaide	1	1	
International staging system Units: Subjects			
Stage I	17	17	
Stage II	4	4	
Stage III	2	2	
Not recorded at diagnosis	17	17	

End points

End points reporting groups

Reporting group title	Bortezomib consolidaion

Reporting group description:

Bortezomib was given at 1.3 mg/m² by subcutaneous injection (or intravenously if the patient did not tolerate subcutaneous injection) on days 1, 8, 15 and 22 of each 4-week cycle. After 3 cycles and approximately (within 4 weeks of) 6 months post ASCT, patients underwent re-staging of their disease. Patients with progressive disease came off protocol.
All other patients continued treatment for a maximum of 8 cycles, as tolerated, and then stopped treatment.
Within 4 weeks of stopping treatment patients underwent re-staging of their disease

Primary: Disease response at 6 months post ASCT

End point title	Disease response at 6 months post ASCT[1]

End point description:

End point type	Primary

End point timeframe:

6 months post ASCT

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 is the proportion of patients in each of the response categories. No specific statistical analysis is required to establish the percentage of patients. This can be calculated using the number of patients who are in the trial and the number of patients in each response category.

End point values	Bortezomib consolidaion			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: Patients				
sCR/CR	5			
VGPR	23			
PR	6			

Statistical analyses

No statistical analyses for this end point

Primary: Disease response at 12 months post ASCT

End point title	Disease response at 12 months post ASCT[2]

End point description:

End point type	Primary

End point timeframe:

12 months post ASCT

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 in each of the response categories. No specific statistical analysis is required to establish the percentage of patients. This can be calculated using the number of patients who are in the trial and the number of patients in each response category.

End point values	Bortezomib consolidaion			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: Patients				
sCR/CR	7			
VGPR	22			

Statistical analyses

No statistical analyses for this end point

Primary: Toxicity

End point title	Toxicity[3]

End point description:

Number of patients suffering grade 3 or 4 toxicity as assessed by the NCI Common Terminology for Adverse Events (v3.0)

End point type	Primary

End point timeframe:

Between informed consent and 30 days post last trial treatment

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 primary endpoint is the number 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.

End point values	Bortezomib consolidaion			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: Patients				
Patients reporting grade 3 or 4 AE	13			
Patients not reporting grade 3 or 4 AE	26			

Statistical analyses

No statistical analyses for this end point

Secondary: MRD status at 6 months post ASCT

End point title	MRD status at 6 months post ASCT

End point description:

End point type	Secondary

End point timeframe:

6 months post ASCT

End point values	Bortezomib consolidaion			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: Patients				
MRD negative	9			
MRD positive	10			

Statistical analyses

No statistical analyses for this end point

Secondary: MRD status at 12 months post ASCT

End point title	MRD status at 12 months post ASCT

End point description:

End point type	Secondary

End point timeframe:

12 months post ASCT

End point values	Bortezomib consolidaion			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: Patients				
MRD negative	13			
MRD positive	6			

Statistical analyses

No statistical analyses for this end point

Secondary: Median progression free survival from ASCT

End point title	Median progression free survival from ASCT

End point description:

End point type	Secondary

End point timeframe:

Endpoint was analysed once all the trial data had been entered

End point values	Bortezomib consolidaion			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: Number of months				
median (confidence interval 95%)				
Number of months	41.6 (37.3 to 41.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life

End point title	Quality of life

End point description:

Change in quality of life score between baseline and 12 months post ASCT

End point type	Secondary

End point timeframe:

Between baseline and 12 months post ASCT

End point values	Bortezomib consolidaion			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Quality of life score				
median (confidence interval 95%)				
Change in quality of life score	0.0 (-16.7 to 33.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Outcome of relapse - salvage regimen

End point title	Outcome of relapse - salvage regimen

End point description:

Salvage regimens used for patients who relapsed

End point type	Secondary

End point timeframe:
Duration of trial

End point values	Bortezomib consolidaion			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: Patients				
Bortezomib based regimen	13			
Carfilzomib based regimen	5			
Not started second line therapy	10			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival from the start of second line therapy

End point title	Progression free survival from the start of second line therapy

End point description:
Progression free survival from the start of second line therapy

End point type	Secondary

End point timeframe:
Duration of trial

End point values	Bortezomib consolidaion			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Months				
median (confidence interval 95%)				
Number of months	17.7 (13.7 to 21.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Best response to salvage regimen

End point title	Best response to salvage regimen

End point description:
Response with bortezomib salvage regimen

End point type	Secondary

End point timeframe:

Salvage regimen assessment

End point values	Bortezomib consolidaion			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: Patients				
VGPR	6			
PR	4			
SD	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Second progression free survival

End point title	Second progression free survival

End point description:

Second progression free survival from start of second line therapy

End point type	Secondary

End point timeframe:

Whole trial

End point values	Bortezomib consolidaion			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Months				
median (confidence interval 95%)				
Months	17.7 (13.7 to 21.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Second progression free survival

End point title	Second progression free survival

End point description:

Second progression free survival from registration

End point type	Secondary

End point timeframe:
Whole trial

End point values	Bortezomib consolidaion			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Months				
median (confidence interval 95%)				
Months	71.4 (54.1 to 88.8)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Between informed consent and 30 days post last trial treatment administration

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

Dictionary used

Dictionary name	NCI-CTCAE
Dictionary version	3.0

Reporting groups

Reporting group title	Bortezomib

Reporting group description: -

Serious adverse events	Bortezomib		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 39 (10.26%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events			
Cardiac disorders			
Supraventricular tachycardia			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			

subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Infection with normal ANC	Additional description: Infection with normal ANC was a grade 2 AE. Reported as SAE due to previous drug overdose for this patient.		
subjects affected / exposed	1 / 39 (2.56%)		
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	Bortezomib		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 39 (100.00%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	4		
Nervous system disorders			
Neuropathy (sensory)			
subjects affected / exposed	24 / 39 (61.54%)		
occurrences (all)	108		
Dizziness			
subjects affected / exposed	7 / 39 (17.95%)		
occurrences (all)	9		
Neuropathy (autonomic)			

subjects affected / exposed	6 / 39 (15.38%)		
occurrences (all)	6		
Peripheral neuropathy (motor)			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Cranial - various motor			
subjects affected / exposed	6 / 39 (15.38%)		
occurrences (all)	9		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	31 / 39 (79.49%)		
occurrences (all)	121		
Flu like symptoms			
subjects affected / exposed	4 / 39 (10.26%)		
occurrences (all)	4		
Injection site reaction			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	4		
Hot flushes			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	3		
Blood and lymphatic system disorders			
Platelets			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	6		
Neutrophils			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	3		
Ear and labyrinth disorders			
Hearing			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Eye disorders			
Vision - blurred vision			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		

Dry eye syndrome subjects affected / exposed occurrences (all) Watery eye subjects affected / exposed occurrences (all)	 3 / 39 (7.69%) 4 3 / 39 (7.69%) 6		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Pain - abdominal subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 18 / 39 (46.15%) 58 15 / 39 (38.46%) 27 14 / 39 (35.90%) 26 11 / 39 (28.21%) 18 6 / 39 (15.38%) 6		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all)	 7 / 39 (17.95%) 8 3 / 39 (7.69%) 3		
Skin and subcutaneous tissue disorders Dermatology/Skin - other subjects affected / exposed occurrences (all) Rash: Erythema multiforme subjects affected / exposed occurrences (all)	 11 / 39 (28.21%) 26 2 / 39 (5.13%) 2		

Pruritus subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2		
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 5		
Musculoskeletal and connective tissue disorders Pain - Joint subjects affected / exposed occurrences (all) Pain - back subjects affected / exposed occurrences (all)	9 / 39 (23.08%) 13 5 / 39 (12.82%) 9		
Infections and infestations Infection - Pulmonary/Upper Respiratory subjects affected / exposed occurrences (all) Infection - lung subjects affected / exposed occurrences (all) Infections - other subjects affected / exposed occurrences (all) Infection - mucosa subjects affected / exposed occurrences (all) Infection - conjunctiva subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	10 / 39 (25.64%) 12 7 / 39 (17.95%) 7 5 / 39 (12.82%) 5 3 / 39 (7.69%) 4 2 / 39 (5.13%) 2 2 / 39 (5.13%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 October 2009	To show changes from protocol version 1.0 to protocol v2.1 a) Clarified that Derralyn Hughes is the Principal Investigator at the Royal Free Hospital site (Section 1). b) Updated the protocol exclusion criteria to accurately reflect the SmPc (section 11.2). c) Clarified that the hospital pharmacy would re-constitute the IMP, rather than the pharmacist, as a pharmacy technician might be responsible for reconstitution as per standard hospital practice (section 13.1.1). d) Clarified in the protocol the total number of visits required for patients (section 15). e) The protocol was amended so as to clarify the purpose of the the inclusion of the control group and its impact on data analysis (section 26.3). f) Provided in the protocol a statement which clearly defines Janssen Cilag's involvement in the proposed research (Section 33). g) Changed the formula used to calculate the body surface area to the Dubois formula (Appendix 4)
17 December 2009	Updated IRAS form with details of radiation dose (section 3, Part B)
14 June 2010	Notification of urgent safety measure - changed the days of dosing in each cycle from Days 1, 4, 8 and 11 to Days 1, 8, 15 and 22, as we consider that treatment regime will be better tolerated. Also notified the MHRA of minor changes made to the protocol (ie to create version 2.2, dated 27 Nov 2009) since the last version they reviewed (ie. version 2.1, dated 7 Aug 2009).
17 September 2010	To submit IMP labels for carton and blister vial for bortezomib
14 January 2011	Temporary halt to recruitment
03 March 2011	Changes made throughout protocol (many for clarification).
09 March 2011	Request to re-start trial
21 November 2011	Change for bortezomib administration from IV to subcut; Amended IMP labels for subcut bortezomib Addition of MRD tests by multiparameter flow cytometry Transfer of administration from UCL JRO to UCL CTC
08 December 2011	Urgent Safety Measure: Trial bortezomib (Velcade) IV stock temporarily used for subcutaneous administration in place of subcutaneous stock that could not be shipped to sites.

18 June 2012	Protocol and CTA were amended to reflect the following changes: • Skeletal survey (CT, MRI, PET) are now optional • Changes to exclusion criteria (bisphosphonate treatment; CYP219 and CYP3A4 inhibitors and inducers) • Intravenous administration of bortezomib brought back for patients who cannot tolerate the subcut administration • Ambiguity in Interim analysis section corrected
25 September 2015	Protocol updated to version 7.0, - Addition of secondary endpoints - Extension of trial follow up period and avoidance of trial closure - Adoption of bortezomib SPC as RSI for both IV and SC, replacing IB and protocol 6.0 Appendix 6.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
31 December 2010	A key member of the trial team, with responsibilities for co-ordination, had recently left. A temporary halt was put in place on 31/12/2010 to allow sufficient time for an appropriate replacement to be put in place. The trial was re-started on 28/02/2011	28 February 2011

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 adverse events

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30460696