# 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<br>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<br>Units: years | | | |
| median | 61 | | |
| full range (min-max) | 43 to 69 | - | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 18 | 18 | |
| Male | 22 | 22 | |
| Disease isotype<br>Units: Subjects | | | |
| IgG | 22 | 22 | |

| | | | |
|---|---|---|---|
| IgA | 9 | 9 | |
| IgD | 1 | 1 | |
| Light chain only | 7 | 7 | |
| Non-secretory | 1 | 1 | |
| Induction regimen<br>Units: Subjects | | | |
| Thalidomide-containing | 35 | 35 | |
| Idarubicin/dexamethasone | 4 | 4 | |
| Idarubicin\dexamethasone\cyclophosphaide | 1 | 1 | |
| International staging system<br>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<br>subjects affected / exposed<br>occurrences (all)<br><br>Watery eye<br>subjects affected / exposed<br>occurrences (all) | <br>3 / 39 (7.69%)<br>4<br><br><br>3 / 39 (7.69%)<br>6 | | |
| Gastrointestinal disorders<br>Constipation<br>subjects affected / exposed<br>occurrences (all)<br><br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)<br><br>Nausea<br>subjects affected / exposed<br>occurrences (all)<br><br>Pain - abdominal<br>subjects affected / exposed<br>occurrences (all)<br><br>Vomiting<br>subjects affected / exposed<br>occurrences (all) | <br><br>18 / 39 (46.15%)<br>58<br><br><br>15 / 39 (38.46%)<br>27<br><br><br>14 / 39 (35.90%)<br>26<br><br><br>11 / 39 (28.21%)<br>18<br><br><br>6 / 39 (15.38%)<br>6 | | |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)<br><br>Dyspnoea<br>subjects affected / exposed<br>occurrences (all) | <br><br>7 / 39 (17.95%)<br>8<br><br><br>3 / 39 (7.69%)<br>3 | | |
| Skin and subcutaneous tissue disorders<br>Dermatology/Skin - other<br>subjects affected / exposed<br>occurrences (all)<br><br>Rash: Erythema multiforme<br>subjects affected / exposed<br>occurrences (all) | <br><br>11 / 39 (28.21%)<br>26<br><br><br>2 / 39 (5.13%)<br>2 | | |

| | | | |
|---|---|---|---|
| Pruritus<br>subjects affected / exposed<br>occurrences (all) | 2 / 39 (5.13%)<br>2 | | |
| Psychiatric disorders<br>Depression<br>subjects affected / exposed<br>occurrences (all) | 2 / 39 (5.13%)<br>5 | | |
| Musculoskeletal and connective tissue disorders<br>Pain - Joint<br>subjects affected / exposed<br>occurrences (all)<br><br>Pain - back<br>subjects affected / exposed<br>occurrences (all) | 9 / 39 (23.08%)<br>13<br><br>5 / 39 (12.82%)<br>9 | | |
| Infections and infestations<br>Infection - Pulmonary/Upper Respiratory<br>subjects affected / exposed<br>occurrences (all)<br><br>Infection - lung<br>subjects affected / exposed<br>occurrences (all)<br><br>Infections - other<br>subjects affected / exposed<br>occurrences (all)<br><br>Infection - mucosa<br>subjects affected / exposed<br>occurrences (all)<br><br>Infection - conjunctiva<br>subjects affected / exposed<br>occurrences (all)<br><br>Urinary tract infection<br>subjects affected / exposed<br>occurrences (all) | 10 / 39 (25.64%)<br>12<br><br>7 / 39 (17.95%)<br>7<br><br>5 / 39 (12.82%)<br>5<br><br>3 / 39 (7.69%)<br>4<br><br>2 / 39 (5.13%)<br>2<br><br>2 / 39 (5.13%)<br>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<br>a) Clarified that Derralyn Hughes is the Principal Investigator at the Royal Free Hospital site (Section 1).<br>b) Updated the protocol exclusion criteria to accurately reflect the SmPc (section 11.2).<br>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).<br>d) Clarified in the protocol the total number of visits required for patients (section 15).<br>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).<br>f) Provided in the protocol a statement which clearly defines Janssen Cilag's involvement in the proposed research (Section 33).<br>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.<br>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<br>Addition of MRD tests by multiparameter flow cytometry<br>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. |

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

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| Serious and non serious AEs are listed under non-serious adverse events |

Notes:

## Online references

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