



## Clinical trial results:

### Optimising Renal outcome in Myeloma renal failure

**A pilot study of Thalidomide, Bendamustine, and Dexamethasone (TBD) vs Bortezomib, Bendamustine, and Dexamethasone (BBD) in patients with renal failure defined as a GFR below 30 mls/ min.**

## Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2012-003947-31 |
| Trial protocol           | GB             |
| Global end of trial date | 20 April 2020  |

## Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 23 May 2021  |
| First version publication date | 23 May 2021  |

## Trial information

### Trial identification

|                       |                  |
|-----------------------|------------------|
| Sponsor protocol code | 26866138-MMY2070 |
|-----------------------|------------------|

### Additional study identifiers

|                                    |                |
|------------------------------------|----------------|
| ISRCTN number                      | ISRCTN32505664 |
| ClinicalTrials.gov id (NCT number) | NCT02424851    |
| WHO universal trial number (UTN)   | -              |

Notes:

## Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Oxford University Hospitals NHS Foundation Trust  |
| Sponsor organisation address | Research & Development Department, Joint Research Office, Block 60, Churchill Hospital, Oxford, United Kingdom, OX3 7LE |
| Public contact               | Dr Karthik Ramasamy, Oxford University Hospitals NHS Trust, 44 01865235882, kramasamy@nhs.net                           |
| Scientific contact           | Dr Karthik Ramasamy, Oxford University Hospitals NHS Trust, 44 01865235882, kramasamy@nhs.net                           |

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                       | 01 March 2021 |
| Is this the analysis of the primary completion data? | Yes           |
| Primary completion date                              | 20 April 2020 |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 20 April 2020 |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

The primary objectives is to compare the amount of serum free light chain circulating in the body, the rate of renal recovery and overall survival in response to two cycles of therapy with either thalidomide or bortezomib in patients presenting with myeloma and renal failure.

The co-primary objective is to determine if the response to treatment of the myeloma tumour burden is mirrored in the renal response at the end of cycle 4.

Protection of trial subjects:

tbc

Background therapy: -

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 13 January 2014 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | No              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 31 |
| Worldwide total number of subjects   | 31                 |
| 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) | 0  |
| From 65 to 84 years  | 29 |
| 85 years and over    | 2  |

## Subject disposition

### Recruitment

Recruitment details:

In total 88 patients were screened for the trial, of which 31 patients were consented and randomised across 7 sites in the UK by the 9th March 2019.

### Pre-assignment

Screening details:

In total 88 patients were screened for the trial, 57 patients were screen failures. Most frequent reasons for screen failure were participant fragility or renal function improvement.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall trial (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Randomised - controlled        |
| Blinding used                | Not blinded                    |

### Arms

|                              |  |
|------------------------------|--|
| Are arms mutually exclusive? | Yes  |
| <b>Arm title</b>             | Bortezomib, Bendamustine and Dexamethasone |

Arm description:

Bortezomib, Bendamustine and Dexamethasone

|  |  |
|--|--|
| Arm type                               | Active comparator  |
| Investigational medicinal product name | Bortezomib   |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Powder for concentrate for solution for injection/infusion |
| Routes of administration               | Intravenous use  |

Dosage and administration details:

1.3 mg/m<sup>2</sup>

|                  |   |
|------------------|---|
| <b>Arm title</b> | Thalidomide, Bendamustine and Dexamethasone |
|------------------|---|

Arm description:

Thalidomide, Bendamustine and Dexamethasone

|  |  |
|--|--|
| Arm type                               | Experimental                                     |
| Investigational medicinal product name | Thalidomide                                      |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Powder for concentrate for solution for infusion |
| Routes of administration               | Intramuscular and intravenous use                |

Dosage and administration details:

2.5 mg/ml

| <b>Number of subjects in period 1</b> | Bortezomib,<br>Bendamustine and<br>Dexamethasone | Thalidomide,<br>Bendamustine and<br>Dexamethasone |
|---------------------------------------|--|---|
| Started                               | 16   | 15  |
| Completed                             | 16   | 15  |

## Baseline characteristics

### Reporting groups

|   |   |
|---|---|
| Reporting group title   | Bortezomib, Bendamustine and Dexamethasone  |
| Reporting group description:<br>Bortezomib, Bendamustine and Dexamethasone  |   |
| Reporting group title   | Thalidomide, Bendamustine and Dexamethasone |
| Reporting group description:<br>Thalidomide, Bendamustine and Dexamethasone |   |

| Reporting group values                | Bortezomib,<br>Bendamustine and<br>Dexamethasone | Thalidomide,<br>Bendamustine and<br>Dexamethasone | Total |
|---------------------------------------|--|---|-------|
| Number of subjects                    | 16   | 15  | 31    |
| Age categorical<br>Units: Subjects    |  |   |       |
| 70 years and under                    | 8  | 8   | 16    |
| Over 70 years                         | 8  | 7   | 15    |
| Gender categorical<br>Units: Subjects |  |   |       |
| Female                                | 8  | 6   | 14    |
| Male                                  | 8  | 9   | 17    |

## End points

### End points reporting groups

|                              |   |
|------------------------------|---|
| Reporting group title        | Bortezomib, Bendamustine and Dexamethasone  |
| Reporting group description: | Bortezomib, Bendamustine and Dexamethasone  |
| Reporting group title        | Thalidomide, Bendamustine and Dexamethasone |
| Reporting group description: | Thalidomide, Bendamustine and Dexamethasone |

### Primary: Serum Free Light Chain Response to Treatment - Defined as >50% Reduction From Baseline in sFLC

|                        |  |
|------------------------|--|
| End point title        | Serum Free Light Chain Response to Treatment - Defined as >50% Reduction From Baseline in sFLC |
| End point description: |  |
| End point type         | Primary  |
| End point timeframe:   | End of week 6 (after receiving two cycles of therapy)  |

| End point values            | Bortezomib, Bendamustine and Dexamethasone | Thalidomide, Bendamustine and Dexamethasone |  |  |
|-----------------------------|--|---|--|--|
| Subject group type          | Reporting group                            | Reporting group                             |  |  |
| Number of subjects analysed | 16   | 14  |  |  |
| Units: Participants         | 13   | 3   |  |  |

### Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Primary outcome 1  |
| Comparison groups                       | Bortezomib, Bendamustine and Dexamethasone v Thalidomide, Bendamustine and Dexamethasone |
| Number of subjects included in analysis | 30   |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | other  |
| P-value                                 | = 0.006  |
| Method                                  | Fisher exact   |

### Primary: Renal Response to Treatment Using the International Myeloma Working Group (IMWG) Renal Response Criteria

|                 |   |
|-----------------|---|
| End point title | Renal Response to Treatment Using the International Myeloma |
|-----------------|---|

End point description:

End point type Primary

End point timeframe:

End of week 12 (after receiving 4 cycles of therapy)

| End point values            | Bortezomib,<br>Bendamustine<br>and<br>Dexamethasone | Thalidomide,<br>Bendamustine<br>and<br>Dexamethasone |  |  |
|-----------------------------|---|--|--|--|
| Subject group type          | Reporting group                                     | Reporting group                                      |  |  |
| Number of subjects analysed | 16  | 15   |  |  |
| Units: Participants         |   |  |  |  |
| Complete/partial response   | 5   | 1  |  |  |
| Minor response              | 3   | 7  |  |  |
| No response                 | 3   | 1  |  |  |
| Not evaluable               | 5   | 6  |  |  |

**Statistical analyses**

|   |  |
|---|--|
| Statistical analysis title              | Primary outcome 2  |
| Comparison groups                       | Bortezomib, Bendamustine and Dexamethasone v Thalidomide, Bendamustine and Dexamethasone |
| Number of subjects included in analysis | 31   |
| Analysis specification                  | Post-hoc   |
| Analysis type                           | other  |
| P-value                                 | = 0.02   |
| Method                                  | Fisher exact   |

**Secondary: Overall survival**

End point title Overall survival

End point description:

End point type Secondary

End point timeframe:

1 month post end of treatment and 1 year post randomisation



| End point values            | Bortezomib, Bendamustine and Dexamethasone | Thalidomide, Bendamustine and Dexamethasone |  |  |
|-----------------------------|--|---|--|--|
| Subject group type          | Reporting group                            | Reporting group                             |  |  |
| Number of subjects analysed | 16   | 15  |  |  |
| Units: Participants         | 9  | 13  |  |  |

### Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Secondary outcome 2  |
| Comparison groups                       | Bortezomib, Bendamustine and Dexamethasone v Thalidomide, Bendamustine and Dexamethasone |
| Number of subjects included in analysis | 31   |
| Analysis specification                  | Post-hoc   |
| Analysis type                           | other  |
| P-value                                 | = 0.31   |
| Method                                  | Logrank  |

### Secondary: Haematological and Non-haematological Toxicity in Both Treatment Arms

|   |   |
|---|---|
| End point title   | Haematological and Non-haematological Toxicity in Both Treatment Arms |
| End point description:  |   |
| End point type  | Secondary   |
| End point timeframe:  |   |
| End of weeks 3, 6, 9, 12 (after receiving 4 cycles of therapy), 30 days after final treatment and 12 months after randomisation |   |

| End point values            | Bortezomib, Bendamustine and Dexamethasone | Thalidomide, Bendamustine and Dexamethasone |  |  |
|-----------------------------|--|---|--|--|
| Subject group type          | Reporting group                            | Reporting group                             |  |  |
| Number of subjects analysed | 16   | 15  |  |  |
| Units: Events               |  |   |  |  |
| Serious adverse events      | 2  | 0   |  |  |
| Adverse events              | 3  | 6   |  |  |

### Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Secondary outcome 4  |
| Comparison groups                       | Bortezomib, Bendamustine and Dexamethasone v Thalidomide, Bendamustine and Dexamethasone |
| Number of subjects included in analysis | 31   |
| Analysis specification                  | Post-hoc   |
| Analysis type                           | other  |
| P-value                                 | = 0.48 <sup>[1]</sup>  |
| Method                                  | Fisher exact   |

Notes:

[1] - No statistically significant differences were detected between SAEs or AEs by treatment arm, Fisher's Exact p=0.48 and p=0.25 respectively.

### **Secondary: Comparison of Renal Response, Using the IMWG Renal Response Criteria, at the End of the Second and Fourth Cycles of Therapy**

|                 |   |
|-----------------|---|
| End point title | Comparison of Renal Response, Using the IMWG Renal Response Criteria, at the End of the Second and Fourth Cycles of Therapy |
|-----------------|---|

End point description:

|                       |           |
|-----------------------|-----------|
| End point type        | Secondary |
| End point timeframe:  |           |
| End of weeks 6 and 12 |           |

| <b>End point values</b>     | Bortezomib, Bendamustine and Dexamethasone | Thalidomide, Bendamustine and Dexamethasone |  |  |
|-----------------------------|--|---|--|--|
| Subject group type          | Reporting group                            | Reporting group                             |  |  |
| Number of subjects analysed | 15   | 13  |  |  |
| Units: Participants         |  |   |  |  |
| Partial response            | 2  | 0   |  |  |
| Minor response              | 9  | 7   |  |  |
| No response                 | 4  | 6   |  |  |

### **Statistical analyses**

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Secondary outcome 3  |
| Comparison groups                       | Bortezomib, Bendamustine and Dexamethasone v Thalidomide, Bendamustine and Dexamethasone |
| Number of subjects included in analysis | 28   |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | other  |
| P-value                                 | = 0.45   |
| Method                                  | Fisher exact   |

## Secondary: Quality of Life Measured by the EQ-5D-3L Questionnaire

|                 |  |
|-----------------|--|
| End point title | Quality of Life Measured by the EQ-5D-3L Questionnaire |
|-----------------|--|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

End of week 1 cycles 1-4 and at 1 month follow up

| End point values                     | Bortezomib, Bendamustine and Dexamethasone | Thalidomide, Bendamustine and Dexamethasone |  |  |
|--------------------------------------|--|---|--|--|
| Subject group type                   | Reporting group                            | Reporting group                             |  |  |
| Number of subjects analysed          | 8  | 9   |  |  |
| Units: Score on a scale              |  |   |  |  |
| arithmetic mean (standard deviation) |  |   |  |  |
| Baseline                             | 0.72 (± 0.15)                              | 0.69 (± 0.35)                               |  |  |
| 1 month follow up                    | 0.69 (± 0.19)                              | 0.80 (± 0.28)                               |  |  |

## Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Secondary outcome 5  |
| Comparison groups                       | Bortezomib, Bendamustine and Dexamethasone v Thalidomide, Bendamustine and Dexamethasone |
| Number of subjects included in analysis | 17   |
| Analysis specification                  | Post-hoc   |
| Analysis type                           | other  |
| P-value                                 | = 0.33   |
| Method                                  | t-test, 2-sided  |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From randomisation to 30 days following last administration of IMP

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |       |
|-----------------|-------|
| Dictionary name | CTCAE |
|-----------------|-------|

|                    |     |
|--------------------|-----|
| Dictionary version | 4.0 |
|--------------------|-----|

### Reporting groups

|                       |  |
|-----------------------|--|
| Reporting group title | Bortezomib, bendamustine and dexamethasone |
|-----------------------|--|

Reporting group description: -

|                       |   |
|-----------------------|---|
| Reporting group title | Thalidomide, bendamustine and dexamethasone |
|-----------------------|---|

Reporting group description: -

| <b>Serious adverse events</b>                        | Bortezomib,<br>bendamustine and<br>dexamethasone | Thalidomide,<br>bendamustine and<br>dexamethasone |  |
|--|--|---|--|
| Total subjects affected by serious adverse events    |  |   |  |
| subjects affected / exposed                          | 11 / 16 (68.75%)                                 | 9 / 15 (60.00%)                                   |  |
| number of deaths (all causes)                        | 7  | 2   |  |
| number of deaths resulting from adverse events       |  |   |  |
| Vascular disorders                                   |  |   |  |
| Hypotension  |  |   |  |
| subjects affected / exposed                          | 1 / 16 (6.25%)                                   | 1 / 15 (6.67%)                                    |  |
| occurrences causally related to treatment / all      | 0 / 1  | 0 / 1   |  |
| deaths causally related to treatment / all           | 0 / 0  | 0 / 0   |  |
| Thromboembolic event                                 |  |   |  |
| subjects affected / exposed                          | 0 / 16 (0.00%)                                   | 1 / 15 (6.67%)                                    |  |
| occurrences causally related to treatment / all      | 0 / 0  | 0 / 1   |  |
| deaths causally related to treatment / all           | 0 / 0  | 0 / 0   |  |
| General disorders and administration site conditions |  |   |  |
| Edema limbs  |  |   |  |
| subjects affected / exposed                          | 1 / 16 (6.25%)                                   | 0 / 15 (0.00%)                                    |  |
| occurrences causally related to treatment / all      | 1 / 1  | 0 / 0   |  |
| deaths causally related to treatment / all           | 0 / 0  | 0 / 0   |  |
| Fatigue  |  |   |  |

|   |                 |                |  |
|---|-----------------|----------------|--|
| subjects affected / exposed                     | 0 / 16 (0.00%)  | 1 / 15 (6.67%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| fever   |                 |                |  |
| subjects affected / exposed                     | 0 / 16 (0.00%)  | 1 / 15 (6.67%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 3          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Respiratory, thoracic and mediastinal disorders |                 |                |  |
| Dyspnea   |                 |                |  |
| subjects affected / exposed                     | 0 / 16 (0.00%)  | 1 / 15 (6.67%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Atelectasis                                     |                 |                |  |
| subjects affected / exposed                     | 0 / 16 (0.00%)  | 1 / 15 (6.67%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Psychiatric disorders                           |                 |                |  |
| Delirium  |                 |                |  |
| subjects affected / exposed                     | 0 / 16 (0.00%)  | 1 / 15 (6.67%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Injury, poisoning and procedural complications  |                 |                |  |
| Fall  |                 |                |  |
| subjects affected / exposed                     | 2 / 16 (12.50%) | 0 / 15 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Cardiac disorders                               |                 |                |  |
| Atrial fibrillation                             |                 |                |  |
| subjects affected / exposed                     | 2 / 16 (12.50%) | 0 / 15 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Supraventricular tachycardia                    |                 |                |  |

|   |                 |                |  |
|---|-----------------|----------------|--|
| subjects affected / exposed                     | 0 / 16 (0.00%)  | 1 / 15 (6.67%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1          |  |
| <b>Nervous system disorders</b>                 |                 |                |  |
| Dizziness                                       |                 |                |  |
| subjects affected / exposed                     | 0 / 16 (0.00%)  | 1 / 15 (6.67%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Stroke  |                 |                |  |
| subjects affected / exposed                     | 0 / 16 (0.00%)  | 1 / 15 (6.67%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 1          |  |
| Syncope   |                 |                |  |
| subjects affected / exposed                     | 1 / 16 (6.25%)  | 0 / 15 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Transient ischemic attacks                      |                 |                |  |
| subjects affected / exposed                     | 1 / 16 (6.25%)  | 0 / 15 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| <b>Blood and lymphatic system disorders</b>     |                 |                |  |
| Anaemia   |                 |                |  |
| subjects affected / exposed                     | 2 / 16 (12.50%) | 0 / 15 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| Febrile neutropenia                             |                 |                |  |
| subjects affected / exposed                     | 0 / 16 (0.00%)  | 1 / 15 (6.67%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |
| <b>Gastrointestinal disorders</b>               |                 |                |  |
| Diarrhoea                                       |                 |                |  |
| subjects affected / exposed                     | 2 / 16 (12.50%) | 1 / 15 (6.67%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| Vomiting  |                |                 |  |
| subjects affected / exposed                     | 1 / 16 (6.25%) | 1 / 15 (6.67%)  |  |
| occurrences causally related to treatment / all | 0 / 1          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Skin and subcutaneous tissue disorders          |                |                 |  |
| Rash maculo-papular                             |                |                 |  |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 15 (6.67%)  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Skin infection                                  |                |                 |  |
| subjects affected / exposed                     | 1 / 16 (6.25%) | 0 / 15 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Renal and urinary disorders                     |                |                 |  |
| Chronic kidney disease                          |                |                 |  |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 2 / 15 (13.33%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Hematuria                                       |                |                 |  |
| subjects affected / exposed                     | 0 / 16 (0.00%) | 1 / 15 (6.67%)  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                |                 |  |
| Back pain                                       |                |                 |  |
| subjects affected / exposed                     | 1 / 16 (6.25%) | 1 / 15 (6.67%)  |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Flank pain                                      |                |                 |  |
| subjects affected / exposed                     | 1 / 16 (6.25%) | 0 / 15 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Infections and infestations                     |                |                 |  |
| Bone infection                                  |                |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 16 (6.25%)  | 0 / 15 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bronchial infection                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 16 (6.25%)  | 0 / 15 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infection                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 16 (0.00%)  | 1 / 15 (6.67%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lung infection                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 16 (6.25%)  | 3 / 15 (20.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 2 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sepsis  |                 |                 |  |
| subjects affected / exposed                     | 2 / 16 (12.50%) | 0 / 15 (0.00%)  |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Upper respiratory infection                     |                 |                 |  |
| subjects affected / exposed                     | 2 / 16 (12.50%) | 0 / 15 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary tract infection                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 16 (0.00%)  | 1 / 15 (6.67%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| Hyperkalemia                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 16 (0.00%)  | 1 / 15 (6.67%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |



Frequency threshold for reporting non-serious adverse events: 0 %

| <b>Non-serious adverse events</b>                                   | <b>Bortezomib,<br/>bendamustine and<br/>dexamethasone</b> | <b>Thalidomide,<br/>bendamustine and<br/>dexamethasone</b> |  |
|---|---|--|--|
| Total subjects affected by non-serious adverse events               |   |  |  |
| subjects affected / exposed   | 15 / 16 (93.75%)  | 11 / 15 (73.33%)   |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |   |  |  |
| labial cyst   |   |  |  |
| subjects affected / exposed   | 1 / 16 (6.25%)  | 0 / 15 (0.00%)   |  |
| occurrences (all)   | 1   | 0  |  |
| Vascular disorders  |   |  |  |
| Hypertension  |   |  |  |
| subjects affected / exposed   | 0 / 16 (0.00%)  | 1 / 15 (6.67%)   |  |
| occurrences (all)   | 0   | 1  |  |
| Hypotension   |   |  |  |
| subjects affected / exposed   | 0 / 16 (0.00%)  | 1 / 15 (6.67%)   |  |
| occurrences (all)   | 0   | 1  |  |
| Superficial thrombophlebitis  |   |  |  |
| subjects affected / exposed   | 0 / 16 (0.00%)  | 1 / 15 (6.67%)   |  |
| occurrences (all)   | 0   | 1  |  |
| Thromboembolic event  |   |  |  |
| subjects affected / exposed   | 0 / 16 (0.00%)  | 1 / 15 (6.67%)   |  |
| occurrences (all)   | 0   | 1  |  |
| General disorders and administration site conditions                |   |  |  |
| Fever   |   |  |  |
| subjects affected / exposed   | 1 / 16 (6.25%)  | 1 / 15 (6.67%)   |  |
| occurrences (all)   | 1   | 1  |  |
| Edema limbs   |   |  |  |
| subjects affected / exposed   | 4 / 16 (25.00%)   | 3 / 15 (20.00%)  |  |
| occurrences (all)   | 4   | 3  |  |
| Fatigue   |   |  |  |
| subjects affected / exposed   | 4 / 16 (25.00%)   | 5 / 15 (33.33%)  |  |
| occurrences (all)   | 4   | 9  |  |
| Infusion site extravasation   |   |  |  |
| subjects affected / exposed   | 0 / 16 (0.00%)  | 1 / 15 (6.67%)   |  |
| occurrences (all)   | 0   | 1  |  |

|   |  |  |  |
|---|--|--|--|
| Pain<br>subjects affected / exposed<br>occurrences (all)  | 0 / 16 (0.00%)<br>0  | 1 / 15 (6.67%)<br>1  |  |
| Respiratory, thoracic and mediastinal disorders<br>Atelectasis<br>subjects affected / exposed<br>occurrences (all)<br><br>Laryngeal hemorrhage<br>subjects affected / exposed<br>occurrences (all)<br><br>Dyspnea<br>subjects affected / exposed<br>occurrences (all)<br><br>Upper respiratory infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Productive cough<br>subjects affected / exposed<br>occurrences (all)<br><br>Cough<br>subjects affected / exposed<br>occurrences (all) | 0 / 16 (0.00%)<br>0<br><br>1 / 16 (6.25%)<br>1<br><br>2 / 16 (12.50%)<br>2<br><br>2 / 16 (12.50%)<br>2<br><br>0 / 16 (0.00%)<br>0<br><br>0 / 16 (0.00%)<br>0 | 1 / 15 (6.67%)<br>4<br><br>0 / 15 (0.00%)<br>0<br><br>1 / 15 (6.67%)<br>1<br><br>1 / 15 (6.67%)<br>1<br><br>1 / 15 (6.67%)<br>1<br><br>1 / 15 (6.67%)<br>1 |  |
| Psychiatric disorders<br>Anxiety<br>subjects affected / exposed<br>occurrences (all)<br><br>Insomnia<br>subjects affected / exposed<br>occurrences (all)  | 1 / 16 (6.25%)<br>1<br><br>1 / 16 (6.25%)<br>1   | 0 / 15 (0.00%)<br>0<br><br>0 / 15 (0.00%)<br>0   |  |
| Investigations<br>Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)<br><br>Alkaline Phosphatase Increased<br>subjects affected / exposed<br>occurrences (all)  | 0 / 16 (0.00%)<br>0<br><br>0 / 16 (0.00%)<br>0   | 1 / 15 (6.67%)<br>1<br><br>1 / 15 (6.67%)<br>1   |  |

|  |                      |                      |  |
|--|----------------------|----------------------|--|
| Weight Loss<br>subjects affected / exposed<br>occurrences (all)  | 1 / 16 (6.25%)<br>1  | 1 / 15 (6.67%)<br>1  |  |
| Neutrophil count decreased<br>subjects affected / exposed<br>occurrences (all)                                 | 3 / 16 (18.75%)<br>3 | 2 / 15 (13.33%)<br>2 |  |
| Creatinine increased<br>subjects affected / exposed<br>occurrences (all)                                       | 0 / 16 (0.00%)<br>0  | 1 / 15 (6.67%)<br>1  |  |
| Lymphocyte count decreased<br>subjects affected / exposed<br>occurrences (all)                                 | 0 / 16 (0.00%)<br>0  | 2 / 15 (13.33%)<br>2 |  |
| White blood cell decreased<br>subjects affected / exposed<br>occurrences (all)                                 | 0 / 16 (0.00%)<br>0  | 2 / 15 (13.33%)<br>2 |  |
| Injury, poisoning and procedural complications<br>Fall<br>subjects affected / exposed<br>occurrences (all)     | 1 / 16 (6.25%)<br>1  | 1 / 15 (6.67%)<br>1  |  |
| Cardiac disorders<br>Left Ventricular systolic dysfunction<br>subjects affected / exposed<br>occurrences (all) | 0 / 16 (0.00%)<br>0  | 1 / 15 (6.67%)<br>1  |  |
| Nervous system disorders<br>Tremor<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 16 (6.25%)<br>1  | 3 / 15 (20.00%)<br>4 |  |
| Syncope<br>subjects affected / exposed<br>occurrences (all)  | 1 / 16 (6.25%)<br>1  | 0 / 15 (0.00%)<br>0  |  |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)  | 2 / 16 (12.50%)<br>2 | 1 / 15 (6.67%)<br>1  |  |
| Peripheral sensory neuropathy<br>subjects affected / exposed<br>occurrences (all)                              | 2 / 16 (12.50%)<br>2 | 2 / 15 (13.33%)<br>5 |  |

|   |                      |                      |  |
|---|----------------------|----------------------|--|
| Paresthesia<br>subjects affected / exposed<br>occurrences (all)         | 2 / 16 (12.50%)<br>2 | 3 / 15 (20.00%)<br>3 |  |
| Presyncope<br>subjects affected / exposed<br>occurrences (all)          | 0 / 16 (0.00%)<br>0  | 1 / 15 (6.67%)<br>1  |  |
| Blood and lymphatic system disorders                                    |                      |                      |  |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)             | 1 / 16 (6.25%)<br>1  | 3 / 15 (20.00%)<br>4 |  |
| Febrile neutropenia<br>subjects affected / exposed<br>occurrences (all) | 0 / 16 (0.00%)<br>0  | 1 / 15 (6.67%)<br>1  |  |
| Eye disorders   |                      |                      |  |
| Conjunctivitis<br>subjects affected / exposed<br>occurrences (all)      | 1 / 16 (6.25%)<br>1  | 0 / 15 (0.00%)<br>0  |  |
| Blurred vision<br>subjects affected / exposed<br>occurrences (all)      | 1 / 16 (6.25%)<br>1  | 0 / 15 (0.00%)<br>0  |  |
| visual disturbance<br>subjects affected / exposed<br>occurrences (all)  | 0 / 16 (0.00%)<br>0  | 1 / 15 (6.67%)<br>1  |  |
| Gastrointestinal disorders  |                      |                      |  |
| Mucositis oral<br>subjects affected / exposed<br>occurrences (all)      | 1 / 16 (6.25%)<br>1  | 0 / 15 (0.00%)<br>0  |  |
| Dyspepsia<br>subjects affected / exposed<br>occurrences (all)           | 1 / 16 (6.25%)<br>1  | 0 / 15 (0.00%)<br>0  |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)            | 3 / 16 (18.75%)<br>3 | 1 / 15 (6.67%)<br>1  |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)              | 4 / 16 (25.00%)<br>5 | 1 / 15 (6.67%)<br>1  |  |
| Diarrhoea   |                      |                      |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| subjects affected / exposed                | 3 / 16 (18.75%) | 2 / 15 (13.33%) |  |
| occurrences (all)                          | 6               | 3               |  |
| Constipation                               |                 |                 |  |
| subjects affected / exposed                | 4 / 16 (25.00%) | 3 / 15 (20.00%) |  |
| occurrences (all)                          | 11              | 3               |  |
| Dysphagia                                  |                 |                 |  |
| subjects affected / exposed                | 0 / 16 (0.00%)  | 1 / 15 (6.67%)  |  |
| occurrences (all)                          | 0               | 1               |  |
| Oral Dysesthesia                           |                 |                 |  |
| subjects affected / exposed                | 0 / 16 (0.00%)  | 1 / 15 (6.67%)  |  |
| occurrences (all)                          | 0               | 1               |  |
| Stomach pain                               |                 |                 |  |
| subjects affected / exposed                | 0 / 16 (0.00%)  | 2 / 15 (13.33%) |  |
| occurrences (all)                          | 0               | 2               |  |
| Skin and subcutaneous tissue disorders     |                 |                 |  |
| Rash maculo-papular                        |                 |                 |  |
| subjects affected / exposed                | 1 / 16 (6.25%)  | 3 / 15 (20.00%) |  |
| occurrences (all)                          | 1               | 8               |  |
| Skin ulceration                            |                 |                 |  |
| subjects affected / exposed                | 1 / 16 (6.25%)  | 0 / 15 (0.00%)  |  |
| occurrences (all)                          | 1               | 0               |  |
| Skin infection                             |                 |                 |  |
| subjects affected / exposed                | 2 / 16 (12.50%) | 1 / 15 (6.67%)  |  |
| occurrences (all)                          | 2               | 1               |  |
| Dry skin                                   |                 |                 |  |
| subjects affected / exposed                | 0 / 16 (0.00%)  | 1 / 15 (6.67%)  |  |
| occurrences (all)                          | 0               | 1               |  |
| Scalp pain                                 |                 |                 |  |
| subjects affected / exposed                | 0 / 16 (0.00%)  | 1 / 15 (6.67%)  |  |
| occurrences (all)                          | 0               | 1               |  |
| Erythroderma                               |                 |                 |  |
| subjects affected / exposed                | 0 / 16 (0.00%)  | 1 / 15 (6.67%)  |  |
| occurrences (all)                          | 0               | 1               |  |
| Palmar-plantae erythrodysesthesia syndrome |                 |                 |  |

|  |                     |                     |  |
|--|---------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all) | 0 / 16 (0.00%)<br>0 | 1 / 15 (6.67%)<br>1 |  |
| Renal and urinary disorders                      |                     |                     |  |
| Acute kidney injury                              |                     |                     |  |
| subjects affected / exposed                      | 0 / 16 (0.00%)      | 2 / 15 (13.33%)     |  |
| occurrences (all)                                | 0                   | 2                   |  |
| Chronic kidney disease                           |                     |                     |  |
| subjects affected / exposed                      | 0 / 16 (0.00%)      | 1 / 15 (6.67%)      |  |
| occurrences (all)                                | 0                   | 1                   |  |
| Musculoskeletal and connective tissue disorders  |                     |                     |  |
| Arthritis  |                     |                     |  |
| subjects affected / exposed                      | 0 / 16 (0.00%)      | 1 / 15 (6.67%)      |  |
| occurrences (all)                                | 0                   | 1                   |  |
| Chest wall pain                                  |                     |                     |  |
| subjects affected / exposed                      | 1 / 16 (6.25%)      | 0 / 15 (0.00%)      |  |
| occurrences (all)                                | 1                   | 0                   |  |
| Back pain  |                     |                     |  |
| subjects affected / exposed                      | 2 / 16 (12.50%)     | 0 / 15 (0.00%)      |  |
| occurrences (all)                                | 3                   | 0                   |  |
| Other  |                     |                     |  |
| subjects affected / exposed                      | 0 / 16 (0.00%)      | 1 / 15 (6.67%)      |  |
| occurrences (all)                                | 0                   | 1                   |  |
| Pain in extremity                                |                     |                     |  |
| subjects affected / exposed                      | 0 / 16 (0.00%)      | 1 / 15 (6.67%)      |  |
| occurrences (all)                                | 0                   | 1                   |  |
| Infections and infestations                      |                     |                     |  |
| Bone infection                                   |                     |                     |  |
| subjects affected / exposed                      | 1 / 16 (6.25%)      | 0 / 15 (0.00%)      |  |
| occurrences (all)                                | 1                   | 0                   |  |
| Bronchial Infection                              |                     |                     |  |
| subjects affected / exposed                      | 1 / 16 (6.25%)      | 0 / 15 (0.00%)      |  |
| occurrences (all)                                | 1                   | 0                   |  |
| Catheter related infection                       |                     |                     |  |
| subjects affected / exposed                      | 1 / 16 (6.25%)      | 0 / 15 (0.00%)      |  |
| occurrences (all)                                | 1                   | 0                   |  |
| Enterocolitis infectious                         |                     |                     |  |

|                                    |                 |                 |  |
|------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed        | 1 / 16 (6.25%)  | 0 / 15 (0.00%)  |  |
| occurrences (all)                  | 1               | 0               |  |
| Mucosal infection                  |                 |                 |  |
| subjects affected / exposed        | 1 / 16 (6.25%)  | 0 / 15 (0.00%)  |  |
| occurrences (all)                  | 1               | 0               |  |
| Papulopustular rash                |                 |                 |  |
| subjects affected / exposed        | 1 / 16 (6.25%)  | 0 / 15 (0.00%)  |  |
| occurrences (all)                  | 1               | 0               |  |
| Lung infection                     |                 |                 |  |
| subjects affected / exposed        | 2 / 16 (12.50%) | 3 / 15 (20.00%) |  |
| occurrences (all)                  | 5               | 5               |  |
| Unknown source                     |                 |                 |  |
| subjects affected / exposed        | 0 / 16 (0.00%)  | 1 / 15 (6.67%)  |  |
| occurrences (all)                  | 0               | 1               |  |
| Oral thrush                        |                 |                 |  |
| subjects affected / exposed        | 0 / 16 (0.00%)  | 2 / 15 (13.33%) |  |
| occurrences (all)                  | 0               | 2               |  |
| Metabolism and nutrition disorders |                 |                 |  |
| Anorexia                           |                 |                 |  |
| subjects affected / exposed        | 1 / 16 (6.25%)  | 0 / 15 (0.00%)  |  |
| occurrences (all)                  | 1               | 0               |  |
| Hypokalemia                        |                 |                 |  |
| subjects affected / exposed        | 1 / 16 (6.25%)  | 0 / 15 (0.00%)  |  |
| occurrences (all)                  | 1               | 0               |  |
| Hyperkalemia                       |                 |                 |  |
| subjects affected / exposed        | 0 / 16 (0.00%)  | 1 / 15 (6.67%)  |  |
| occurrences (all)                  | 0               | 1               |  |
| Hyponatremia                       |                 |                 |  |
| subjects affected / exposed        | 0 / 16 (0.00%)  | 1 / 15 (6.67%)  |  |
| occurrences (all)                  | 0               | 1               |  |

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported