



## Clinical trial results:

### A Randomised Study to Investigate the Efficacy of Bendamustine in Subjects with Indolent Non-Hodgkin's Lymphoma (NHL) Refractory to Rituximab

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2010-022102-41 |
| Trial protocol           | SK ES IT PT PL |
| Global end of trial date | 31 July 2018   |

#### Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1 (current)   |
| This version publication date  | 07 August 2019 |
| First version publication date | 07 August 2019 |

#### Trial information

##### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | BDM3502 |
|-----------------------|---------|

##### Additional study identifiers

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

Notes:

##### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Mundipharma Research Ltd.   |
| Sponsor organisation address | 194-198 Cambridge Science Park, Cambridge, United Kingdom, CB4 0AB                                |
| Public contact               | Clinical Operations, Mundipharma Research Ltd., +44 1223 424900, info@contact-clinical-trials.com |
| Scientific contact           | Clinical Operations, Mundipharma Research Ltd., +44 1223 424900, info@contact-clinical-trials.com |

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                       | 31 July 2018 |
| Is this the analysis of the primary completion data? | Yes          |
| Primary completion date                              | 31 July 2018 |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 31 July 2018 |
| Was the trial ended prematurely?                     | Yes          |

Notes:

## General information about the trial

Main objective of the trial:

The main objective of the study was to compare the efficacy of bendamustine against treatment of physician's choice (TPC) on progression free survival (PFS) in subjects with indolent B-cell in Non-Hodgkin's Lymphoma (NHL) that did not respond (stable disease [SD] or progressive disease [PD]) to rituximab or a rituximab containing regimen during or within 6 months of the previous rituximab treatment.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy:

Medications to treat nausea and vomiting or acquired infections during the study were allowed. Blood products and growth factors were allowed at the discretion of the Investigator.

Evidence for comparator:

Treatment in the reference arm was Treatment of Physician's Choice (TPC) which was defined as any cancer specific therapy, or best supportive care. Treatment was given according to the label and based upon local institutional medical practice and clinical judgement. Treatment was experimental in nature. The use of bendamustine was not permitted during the Treatment Phase.

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 04 November 2011 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |               |
|--------------------------------------|---------------|
| Country: Number of subjects enrolled | Poland: 3     |
| Country: Number of subjects enrolled | Portugal: 9   |
| Country: Number of subjects enrolled | Slovakia: 1   |
| Country: Number of subjects enrolled | Spain: 5      |
| Country: Number of subjects enrolled | Australia: 91 |
| Worldwide total number of subjects   | 109           |
| EEA total number of subjects         | 18            |

Notes:

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**Subjects enrolled per age group**

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|   |    |
|---|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 0  |
| Children (2-11 years)                     | 0  |
| Adolescents (12-17 years)                 | 0  |
| Adults (18-64 years)                      | 48 |
| From 65 to 84 years                       | 59 |
| 85 years and over                         | 2  |

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## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 25 centers in 5 countries.

### Pre-assignment

Screening details:

A total of 109 subjects were enrolled into this study, of which 21 subjects were screen failures (21 due to Non-compliance; 1 due to Subject's choice and 2 due to Other reason). Out of the 88 subjects randomised, 54 subjects completed and 31 subjects discontinued the study due to Adverse Events (21), Administrative (1) and Disease Progression (9).

### Period 1

|                              |                                 |
|------------------------------|---------------------------------|
| Period 1 title               | Overall Period (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> | Bendamustine |
|------------------|--------------|

Arm description:

Subjects received intravenously (IV) bendamustine 120 milligram per meter square (mg/m<sup>2</sup>) on Days 1 and 2, every 21 days up to 6 cycles. However, if a subject was receiving clinical benefit after 6 cycles then a further 2 cycles of bendamustine were administered.

|  |  |
|--|--|
| Arm type                               | Experimental                                     |
| Investigational medicinal product name | Bendamustine                                     |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Powder for concentrate for solution for infusion |
| Routes of administration               | Intravenous use                                  |

Dosage and administration details:

Subjects received intravenously bendamustine 120 mg/m<sup>2</sup>

|                  |                                       |
|------------------|---------------------------------------|
| <b>Arm title</b> | Treatment of Physician's Choice (TPC) |
|------------------|---------------------------------------|

Arm description:

Subjects received treatment of physician's choice which is defined as any cancer specific therapy, or best supportive care. Treatment was given according to the label and based upon local institutional medical practice and clinical judgement. Treatment was not experimental in nature. Bendamustine treatment was not permitted as TPC in the treatment phase.

|  |   |
|--|---|
| Arm type                               | TPC   |
| Investigational medicinal product name | Multiple cancer specific therapy                              |
| Investigational medicinal product code |   |
| Other name                             |   |
| Pharmaceutical forms                   | Powder for concentrate and solution for solution for infusion |
| Routes of administration               | Intravenous use   |

Dosage and administration details:

Variable treatment was given according to the label and based upon local institutional medical practice and clinical judgement.

| Number of subjects in period<br>1[1] | Bendamustine | Treatment of<br>Physician's Choice<br>(TPC) |
|--------------------------------------|--------------|---|
|                                      |              |   |
| Started                              | 58           | 30  |
| Completed                            | 39           | 15  |
| Not completed                        | 19           | 15  |
| Never Treated                        | -            | 3   |
| Administrative                       | 1            | -   |
| Adverse event, non-fatal             | 14           | 7   |
| Disease Progression                  | 4            | 5   |

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Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: A total of 109 subjects were enrolled into this study, of which 21 subjects were screen failures and only 88 subjects randomized.

## Baseline characteristics

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | Bendamustine |
|-----------------------|--------------|

Reporting group description:

Subjects received intravenously (IV) bendamustine 120 milligram per meter square (mg/m<sup>2</sup>) on Days 1 and 2, every 21 days up to 6 cycles. However, if a subject was receiving clinical benefit after 6 cycles then a further 2 cycles of bendamustine were administered.

|                       |                                       |
|-----------------------|---------------------------------------|
| Reporting group title | Treatment of Physician's Choice (TPC) |
|-----------------------|---------------------------------------|

Reporting group description:

Subjects received treatment of physician's choice which is defined as any cancer specific therapy, or best supportive care. Treatment was given according to the label and based upon local institutional medical practice and clinical judgement. Treatment was not experimental in nature. Bendamustine treatment was not permitted as TPC in the treatment phase.

| Reporting group values  | Bendamustine    | Treatment of Physician's Choice (TPC) | Total |
|---|-----------------|---------------------------------------|-------|
| Number of subjects  | 58              | 30                                    | 88    |
| Age categorical<br>Units: Subjects                                      |                 |                                       |       |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 63.8<br>± 11.75 | 65.4<br>± 9.87                        | -     |
| Gender categorical<br>Units: Subjects                                   |                 |                                       |       |
| Female  | 24              | 18                                    | 42    |
| Male  | 34              | 12                                    | 46    |

## End points

### End points reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | Bendamustine |
|-----------------------|--------------|

Reporting group description:

Subjects received intravenously (IV) bendamustine 120 milligram per meter square (mg/m<sup>2</sup>) on Days 1 and 2, every 21 days up to 6 cycles. However, if a subject was receiving clinical benefit after 6 cycles then a further 2 cycles of bendamustine were administered.

|                       |                                       |
|-----------------------|---------------------------------------|
| Reporting group title | Treatment of Physician's Choice (TPC) |
|-----------------------|---------------------------------------|

Reporting group description:

Subjects received treatment of physician's choice which is defined as any cancer specific therapy, or best supportive care. Treatment was given according to the label and based upon local institutional medical practice and clinical judgement. Treatment was not experimental in nature. Bendamustine treatment was not permitted as TPC in the treatment phase.

### Primary: Progression Free Survival (PFS)

|                 |                                 |
|-----------------|---------------------------------|
| End point title | Progression Free Survival (PFS) |
|-----------------|---------------------------------|

End point description:

PFS is defined as time from randomization until disease progression or death due to any cause. For subjects who did not have an event (that is those who were lost to follow-up or who had not progressed at the date of data cut-off), PFS was censored. That is: PFS (days) = Date of progression/death/censoring - Date of randomization + 1. Subjects who did not progress in their disease were censored on the date of their last confirmed assessment. The Intent-to treat (ITT) population included all the subjects who were randomized irrespective of whether or not they actually received medication.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From Day 1 up to end of the study (Approximately up to 7.5 years); Follow up was done every 6 months and 3 months for subjects with and without disease progression respectively.

| End point values                 | Bendamustine        | Treatment of Physician's Choice (TPC) |  |  |
|----------------------------------|---------------------|---------------------------------------|--|--|
| Subject group type               | Reporting group     | Reporting group                       |  |  |
| Number of subjects analysed      | 58                  | 30                                    |  |  |
| Units: months                    |                     |                                       |  |  |
| median (confidence interval 95%) | 18.5 (10.2 to 27.2) | 11.2 (7.1 to 18.7)                    |  |  |

### Statistical analyses

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

|                   |  |
|-------------------|--|
| Comparison groups | Bendamustine v Treatment of Physician's Choice (TPC) |
|-------------------|--|

|   |                   |
|---|-------------------|
| Number of subjects included in analysis | 88                |
| Analysis specification                  | Pre-specified     |
| Analysis type                           | superiority       |
| P-value                                 | = 0.297           |
| Method                                  | Log-Rank test     |
| Parameter estimate                      | Hazard ratio (HR) |
| Point estimate                          | 0.752             |
| Confidence interval                     |                   |
| level                                   | 95 %              |
| sides                                   | 2-sided           |
| lower limit                             | 0.403             |
| upper limit                             | 1.403             |

### Secondary: Percentage of Subjects with Overall Response Rate (ORR)

|                 |   |
|-----------------|---|
| End point title | Percentage of Subjects with Overall Response Rate (ORR) |
|-----------------|---|

End point description:

ORR is defined as Percentage of subjects who confirmed Complete Remission (CR) or Partial Remission (PR) called as responders. Non-responders included subjects with stable disease (SD) or progressive disease (PD). CR is defined as complete disappearance of all detectable clinical evidence of disease and disease related symptoms if present before therapy; all lymph nodes and nodal masses must have regressed on computed tomography (CT) to normal size (less than or equal to [ $\leq$ ] 1.5 centimeter [cm] in their greatest transverse diameter for nodes greater than [ $>$ ] 1.5 cm before therapy). PR is defined as least a 50% decrease in the sum of product of the diameters (SPD) of up to six of largest dominant nodes or nodal masses. A subject was considered to have SD when he or she failed to attain the criteria needed for a CR or PR, but did not fulfill those for PD. The ITT population comprised of all subjects who were randomised irrespective of whether or not they actually received medication.

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

End point timeframe:

From Day 1 up to end of the study (Approximately up to 7.5 years)

| End point values              | Bendamustine    | Treatment of Physician's Choice (TPC) |  |  |
|-------------------------------|-----------------|---------------------------------------|--|--|
| Subject group type            | Reporting group | Reporting group                       |  |  |
| Number of subjects analysed   | 58              | 30                                    |  |  |
| Units: Percentage of subjects |                 |                                       |  |  |
| number (not applicable)       |                 |                                       |  |  |
| ORR                           | 77.6            | 56.7                                  |  |  |
| CR                            | 25.9            | 10.0                                  |  |  |
| PR                            | 51.7            | 46.7                                  |  |  |
| SD                            | 12.1            | 20.0                                  |  |  |
| PD                            | 1.7             | 13.3                                  |  |  |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of Response (DR)

|                 |                           |
|-----------------|---------------------------|
| End point title | Duration of Response (DR) |
|-----------------|---------------------------|

End point description:

DR is defined as time from initial response (CR/PR) to progression or death. Where CR is defined as complete disappearance of all detectable clinical evidence of disease and disease related symptoms if present before therapy; all lymph nodes and nodal masses must have regressed on CT to normal size ( $\leq 1.5$  cm in their greatest transverse diameter for nodes  $> 1.5$  cm before therapy). PR is defined as least a 50% decrease in the sum of product of the diameters of up to six of largest dominant nodes or nodal masses. A subject was considered to have SD when he or she failed to attain the criteria needed for a CR or PR, but did not fulfill those for PD. The ITT population comprised of all subjects who were randomised irrespective of whether or not they actually received medication. Here '99999' signifies not estimable as upper bound not reached.

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

End point timeframe:

From Day 1 up to end of the study (Approximately up to 7.5 years)

| End point values                 | Bendamustine       | Treatment of Physician's Choice (TPC) |  |  |
|----------------------------------|--------------------|---------------------------------------|--|--|
| Subject group type               | Reporting group    | Reporting group                       |  |  |
| Number of subjects analysed      | 58                 | 30                                    |  |  |
| Units: months                    |                    |                                       |  |  |
| median (confidence interval 95%) | 17.5 (8.0 to 21.2) | 10.2 (5.0 to 99999)                   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Overall Survival (OS)

|                 |                       |
|-----------------|-----------------------|
| End point title | Overall Survival (OS) |
|-----------------|-----------------------|

End point description:

OS is defined as time from randomization to death. The ITT population comprised of all subjects who were randomized irrespective of whether or not they actually received medication. Here '99999' in median signifies not estimable median survival time cannot be estimated because this group did not reach at the analysis cut off (survival was greater than 50% in the TPC group at the time of the last analysis), while '99999' in upper bound signifies not estimable as upper bound not reached.

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

End point timeframe:

From Day 1 up to end of the study (Approximately up to 7.5 years)

| End point values                 | Bendamustine         | Treatment of Physician's Choice (TPC) |  |  |
|----------------------------------|----------------------|---------------------------------------|--|--|
| Subject group type               | Reporting group      | Reporting group                       |  |  |
| Number of subjects analysed      | 58                   | 30                                    |  |  |
| Units: months                    |                      |                                       |  |  |
| median (confidence interval 95%) | 38.4 (23.3 to 99999) | 99999 (19.6 to 99999)                 |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects with Treatment Emergent Adverse Events (TEAEs) and Serious Treatment Emergent Adverse Events

|                 |   |
|-----------------|---|
| End point title | Number of Subjects with Treatment Emergent Adverse Events (TEAEs) and Serious Treatment Emergent Adverse Events |
|-----------------|---|

End point description:

An adverse event (AE) is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, including placebo, and which did not necessarily have to have had a causal relationship with treatment. An SAE is any untoward medical occurrence that at any dose that resulted in death, was life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect. TEAEs are defined as new or worsening adverse events with an onset date occurring on or after first dose date of study medication inclusive to 30 days post-last dose. The Safety Population included all subjects who were randomized and who received at least 1 dose of study treatment. Here, 'Number of subjects analysed' signifies the subjects evaluable for this population.

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

End point timeframe:

From Day 1 of treatment administration up to 30 days after last treatment

| End point values                              | Bendamustine    | Treatment of Physician's Choice (TPC) |  |  |
|---|-----------------|---------------------------------------|--|--|
| Subject group type                            | Reporting group | Reporting group                       |  |  |
| Number of subjects analysed                   | 58              | 27                                    |  |  |
| Units: Subjects                               |                 |                                       |  |  |
| TEAE  | 58              | 27                                    |  |  |
| TEAE of CTC grade 3 or 4                      | 44              | 18                                    |  |  |
| Serious TEAE                                  | 27              | 7                                     |  |  |
| TEAE Leading to Death                         | 1               | 0                                     |  |  |
| TEAE Leading to Discontinuation of study drug | 13              | 3                                     |  |  |
| TEAE Leading to Dose Reduction                | 20              | 6                                     |  |  |
| TEAE Leading to Dose Withheld                 | 32              | 10                                    |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in Health Related Quality of Life (HRQL) as Assessed by EuroQol Group (EQ-5D)

|                 |  |
|-----------------|--|
| End point title | Change from Baseline in Health Related Quality of Life (HRQL) as Assessed by EuroQoL Group (EQ-5D) |
|-----------------|--|

End point description:

EQ-5D is an instrument for measuring health outcome and consists of five dimensions: mobility, selfcare, usual activities, pain/discomfort, and anxiety/depression and a visual analog scale (VAS). Each dimension has 3 levels: No problems, Some problems, Severe problems. Responses to the single dimensions will be coded numerically 1 to 3 in order of decreasing health status. Responses to the EQ-5D will be converted into an EQ-5D index, which provides a single summary by weighting the response levels in each dimension. The weighted index constitutes a measure of utility and represents a health state from 0 to 1, where 1 is fullest health. This index will be derived only from patients who have provided a complete 5- response profile. The EQ VAS records the subject's self-rated health where the endpoints are worst imaginable health (score=0) to best imaginable health (score =100). Here 'n' signifies number of subjects analysed for category at specified time point.

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

End point timeframe:

Baseline, Day 63 and Day 126

| End point values                    | Bendamustine     | Treatment of Physician's Choice (TPC) |  |  |
|-------------------------------------|------------------|---------------------------------------|--|--|
| Subject group type                  | Reporting group  | Reporting group                       |  |  |
| Number of subjects analysed         | 58               | 30                                    |  |  |
| Units: Units on a scale             |                  |                                       |  |  |
| least squares mean (standard error) |                  |                                       |  |  |
| Day 63: EQ-5D Index (n=44, 17)      | 0.748 (± 0.0358) | 0.761 (± 0.0552)                      |  |  |
| Day 126: EQ-5D Index (n=29, 9)      | 0.738 (± 0.0305) | 0.847 (± 0.0511)                      |  |  |
| Day 63: EQ-5D VAS (n= 44, 17)       | 62.5 (± 2.91)    | 58.5 (± 4.50)                         |  |  |
| Day 126: EQ-5D VAS (n=28, 9)        | 60.9 (± 3.81)    | 63.2 (± 6.22)                         |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in Health Related Quality of Life as Assessed by European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Version 3.0

|                 |  |
|-----------------|--|
| End point title | Change from Baseline in Health Related Quality of Life as Assessed by European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Version 3.0 |
|-----------------|--|

End point description:

EORTC QLQ-C30 v3 is composed of 2 multi-item scales and single-item measures,: 1) Global scale: health status/quality of life (QoL) 2) Functional scales: physical/role/emotional/cognitive/social; 3) Symptom scales: fatigue/nausea/vomiting/pain/dyspnoea/insomnia/appetite loss/constipation/diarrhoea/financial impact. Global health status/ QoL questions are rated from very poor - excellent on scale of 1-7. All other questions are rated as not at all/a little/quite a bit/very much, coded from 1-4 in decreasing order health status. Each multi-item scales includes a different set of items - with no item repetition. All scales are transformed to have scores ranging from 0-100. High score for functional scale represents high/healthy functioning level, high score for global health status /QoL represents high QoL but high score for a symptom scale/item represents a high level of symptomatology/ problem. Here 'n' signifies number of subjects analysed for category at specified time point.

|                              |           |
|------------------------------|-----------|
| End point type               | Secondary |
| End point timeframe:         |           |
| Baseline, Day 63 and Day 126 |           |

| <b>End point values</b>                      | Bendamustine    | Treatment of Physician's Choice (TPC) |  |  |
|--|-----------------|---------------------------------------|--|--|
| Subject group type                           | Reporting group | Reporting group                       |  |  |
| Number of subjects analysed                  | 58              | 30                                    |  |  |
| Units: Units on a scale                      |                 |                                       |  |  |
| least squares mean (standard error)          |                 |                                       |  |  |
| Day 63: Global health status/QoL (n= 44, 17) | 56.73 (± 3.569) | 58.69 (± 5.610)                       |  |  |
| Day 126: Global health status/QoL (n= 29, 9) | 55.68 (± 3.894) | 64.31 (± 6.558)                       |  |  |
| Day 63: Physical functioning (n= 45, 17)     | 67.13 (± 3.427) | 70.14 (± 5.401)                       |  |  |
| Day 126: Physical functioning (n= 30, 9)     | 68.1 (± 3.449)  | 83.58 (± 5.866)                       |  |  |
| Day 63: Role functioning (n= 45, 17)         | 59.55 (± 4.875) | 62.26 (± 7.683)                       |  |  |
| Day 126: Role functioning (n= 30, 9)         | 55.73 (± 5.461) | 77.24 (± 9.268)                       |  |  |
| Day 63: Emotional functioning (n= 45, 17)    | 75.42 (± 2.715) | 78.06 (± 4.285)                       |  |  |
| Day 126: Emotional functioning (n= 30, 9)    | 80.80 (± 3.340) | 77.01 (± 5.690)                       |  |  |
| Day 63: Cognitive functioning (n= 45, 17)    | 74.03 (± 3.501) | 78.53 (± 5.518)                       |  |  |
| Day 126: Cognitive functioning (n= 30, 9)    | 77.77 (± 4.112) | 85.58 (± 7.023)                       |  |  |
| Day 63: Social functioning (n= 44, 17)       | 61.90 (± 4.787) | 63.61 (± 7.773)                       |  |  |
| Day 126: Social functioning (n= 30, 9)       | 66.28 (± 5.108) | 79.83 (± 9.291)                       |  |  |
| Day 63: Fatigue (n= 45, 17)                  | 51.09 (± 4.294) | 39.86 (± 6.770)                       |  |  |
| Day 126: Fatigue (n= 30, 9)                  | 50.61 (± 4.389) | 26.09 (± 7.487)                       |  |  |
| Day 63: Nausea and vomiting (n= 45, 17)      | 17.61 (± 2.471) | 10.92 (± 3.893)                       |  |  |
| Day 126: Nausea and vomiting (n= 30, 9)      | 8.63 (± 3.005)  | 5.13 (± 5.094)                        |  |  |
| Day 63: Pain (n= 45, 17)                     | 21.89 (± 3.834) | 25.24 (± 6.087)                       |  |  |
| Day 126: Pain (n= 30, 9)                     | 14.06 (± 4.322) | 15.4 (± 7.429)                        |  |  |
| Day 63: Dyspnoea (n= 45, 17)                 | 22.01 (± 3.676) | 14.09 (± 5.816)                       |  |  |
| Day 126: Dyspnoea (n= 30, 9)                 | 25.68 (± 4.689) | 7.79 (± 7.991)                        |  |  |
| Day 63: Insomnia (n= 45, 17)                 | 33.51 (± 3.996) | 41.10 (± 6.299)                       |  |  |
| Day 126: Insomnia (n= 30, 9)                 | 38.49 (± 6.813) | 26.63 (± 11.571)                      |  |  |
| Day 63: Appetite loss (n= 45, 17)            | 30.51 (± 4.398) | 27.36 (± 6.936)                       |  |  |

|  |                 |                 |  |  |
|--|-----------------|-----------------|--|--|
| Day 126: Appetite loss (n= 30, 9)          | 27.51 (± 5.24)  | 11.59 (± 9.057) |  |  |
| Day 63: Constipation (n= 45, 17)           | 29.58 (± 3.671) | 20.67 (± 5.797) |  |  |
| Day 126: Constipation (n= 30, 9)           | 11.12 (± 3.523) | 7.04 (± 5.971)  |  |  |
| Day 63: Diarrhoea (n= 45, 17)              | 17.75 (± 3.680) | 7.20 (± 5.791)  |  |  |
| Day 126: Diarrhoea (n= 30, 9)              | 12.6 (± 3.893)  | 8.24 (± 6.591)  |  |  |
| Day 63: Financial difficulties (n= 44, 17) | 21.21 (± 3.173) | 23.59 (± 4.988) |  |  |
| Day 126: Financial difficulties (n= 30, 9) | 18.89 (± 4.068) | 32.07 (± 6.867) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From Day 1 of treatment administration up to 30 days after last treatment.

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

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 13.1 |
|--------------------|------|

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | Bendamustine |
|-----------------------|--------------|

Reporting group description:

Subjects received intravenously (IV) bendamustine 120 milligram per meter square (mg/m<sup>2</sup>) on Days 1 and 2, every 21 days up to 6 cycles. However, if a subject was receiving clinical benefit after 6 cycles then a further 2 cycles of bendamustine were administered.

|                       |                                       |
|-----------------------|---------------------------------------|
| Reporting group title | Treatment of Physician's Choice (TPC) |
|-----------------------|---------------------------------------|

Reporting group description:

Subjects received treatment of physician's choice which is defined as any cancer specific therapy, or best supportive care. Treatment was given according to the label and based upon local institutional medical practice and clinical judgement. Treatment was not experimental in nature. Bendamustine treatment was not permitted as TPC in the treatment phase.

| <b>Serious adverse events</b>                     | Bendamustine     | Treatment of Physician's Choice (TPC) |  |
|---|------------------|---------------------------------------|--|
| Total subjects affected by serious adverse events |                  |                                       |  |
| subjects affected / exposed                       | 27 / 58 (46.55%) | 7 / 27 (25.93%)                       |  |
| number of deaths (all causes)                     | 1                | 0                                     |  |
| number of deaths resulting from adverse events    | 1                | 0                                     |  |
| Injury, poisoning and procedural complications    |                  |                                       |  |
| Limb injury                                       |                  |                                       |  |
| subjects affected / exposed                       | 1 / 58 (1.72%)   | 0 / 27 (0.00%)                        |  |
| occurrences causally related to treatment / all   | 1 / 1            | 0 / 0                                 |  |
| deaths causally related to treatment / all        | 0 / 0            | 0 / 0                                 |  |
| Vascular disorders                                |                  |                                       |  |
| Circulatory collapse                              |                  |                                       |  |
| subjects affected / exposed                       | 0 / 58 (0.00%)   | 1 / 27 (3.70%)                        |  |
| occurrences causally related to treatment / all   | 0 / 0            | 1 / 1                                 |  |
| deaths causally related to treatment / all        | 0 / 0            | 0 / 0                                 |  |
| Cardiac disorders                                 |                  |                                       |  |
| Atrial fibrillation                               |                  |                                       |  |

|  |                  |                |  |
|--|------------------|----------------|--|
| subjects affected / exposed                          | 1 / 58 (1.72%)   | 1 / 27 (3.70%) |  |
| occurrences causally related to treatment / all      | 1 / 1            | 1 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0          |  |
| Cardio-respiratory arrest                            |                  |                |  |
| subjects affected / exposed                          | 1 / 58 (1.72%)   | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all      | 1 / 1            | 0 / 0          |  |
| deaths causally related to treatment / all           | 1 / 1            | 0 / 0          |  |
| General disorders and administration site conditions |                  |                |  |
| Pyrexia  |                  |                |  |
| subjects affected / exposed                          | 10 / 58 (17.24%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all      | 7 / 11           | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0          |  |
| Fatigue  |                  |                |  |
| subjects affected / exposed                          | 1 / 58 (1.72%)   | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all      | 1 / 1            | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0          |  |
| Oedema peripheral                                    |                  |                |  |
| subjects affected / exposed                          | 0 / 58 (0.00%)   | 1 / 27 (3.70%) |  |
| occurrences causally related to treatment / all      | 0 / 0            | 1 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0          |  |
| Systemic inflammatory response syndrome              |                  |                |  |
| subjects affected / exposed                          | 1 / 58 (1.72%)   | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0          |  |
| Blood and lymphatic system disorders                 |                  |                |  |
| Febrile neutropenia                                  |                  |                |  |
| subjects affected / exposed                          | 5 / 58 (8.62%)   | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all      | 7 / 7            | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0          |  |
| Anaemia  |                  |                |  |
| subjects affected / exposed                          | 3 / 58 (5.17%)   | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all      | 3 / 3            | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0          |  |

|   |                |                |  |
|---|----------------|----------------|--|
| Neutropenia                                     |                |                |  |
| subjects affected / exposed                     | 2 / 58 (3.45%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Immune system disorders                         |                |                |  |
| Anaphylactic reaction                           |                |                |  |
| subjects affected / exposed                     | 1 / 58 (1.72%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Gastrointestinal disorders                      |                |                |  |
| Abdominal pain                                  |                |                |  |
| subjects affected / exposed                     | 1 / 58 (1.72%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Vomiting  |                |                |  |
| subjects affected / exposed                     | 1 / 58 (1.72%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Respiratory, thoracic and mediastinal disorders |                |                |  |
| Chronic obstructive pulmonary disease           |                |                |  |
| subjects affected / exposed                     | 1 / 58 (1.72%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pulmonary oedema                                |                |                |  |
| subjects affected / exposed                     | 0 / 58 (0.00%) | 1 / 27 (3.70%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Musculoskeletal and connective tissue disorders |                |                |  |
| Back pain                                       |                |                |  |
| subjects affected / exposed                     | 1 / 58 (1.72%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Musculoskeletal pain                            |                |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 1 / 58 (1.72%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Infections and infestations</b>              |                |                |  |
| Lower respiratory tract infection               |                |                |  |
| subjects affected / exposed                     | 3 / 58 (5.17%) | 1 / 27 (3.70%) |  |
| occurrences causally related to treatment / all | 3 / 3          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Cellulitis                                      |                |                |  |
| subjects affected / exposed                     | 1 / 58 (1.72%) | 1 / 27 (3.70%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Lobar pneumonia                                 |                |                |  |
| subjects affected / exposed                     | 1 / 58 (1.72%) | 1 / 27 (3.70%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Neutropenic sepsis                              |                |                |  |
| subjects affected / exposed                     | 1 / 58 (1.72%) | 1 / 27 (3.70%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pneumonia                                       |                |                |  |
| subjects affected / exposed                     | 1 / 58 (1.72%) | 1 / 27 (3.70%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Arthritis bacterial                             |                |                |  |
| subjects affected / exposed                     | 1 / 58 (1.72%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Bronchitis viral                                |                |                |  |
| subjects affected / exposed                     | 1 / 58 (1.72%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Cytomegalovirus colitis                         |                |                |  |

|  |                |                |  |
|--|----------------|----------------|--|
| subjects affected / exposed  | 0 / 58 (0.00%) | 1 / 27 (3.70%) |  |
| occurrences causally related to treatment / all                      | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all                           | 0 / 0          | 0 / 0          |  |
| <b>H1N1 influenza</b>  |                |                |  |
| subjects affected / exposed  | 1 / 58 (1.72%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all                      | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all                           | 0 / 0          | 0 / 0          |  |
| <b>Infective exacerbation of chronic obstructive airways disease</b> |                |                |  |
| subjects affected / exposed  | 1 / 58 (1.72%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all                      | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all                           | 0 / 0          | 0 / 0          |  |
| <b>Influenza</b>   |                |                |  |
| subjects affected / exposed  | 1 / 58 (1.72%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all                      | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all                           | 0 / 0          | 0 / 0          |  |
| <b>Postoperative wound infection</b>                                 |                |                |  |
| subjects affected / exposed  | 1 / 58 (1.72%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all                      | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all                           | 0 / 0          | 0 / 0          |  |
| <b>Sepsis</b>  |                |                |  |
| subjects affected / exposed  | 1 / 58 (1.72%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all                      | 2 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all                           | 0 / 0          | 0 / 0          |  |
| <b>Urinary tract infection</b>                                       |                |                |  |
| subjects affected / exposed  | 0 / 58 (0.00%) | 1 / 27 (3.70%) |  |
| occurrences causally related to treatment / all                      | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all                           | 0 / 0          | 0 / 0          |  |
| <b>Metabolism and nutrition disorders</b>                            |                |                |  |
| <b>Hypokalaemia</b>  |                |                |  |
| subjects affected / exposed  | 1 / 58 (1.72%) | 0 / 27 (0.00%) |  |
| occurrences causally related to treatment / all                      | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all                           | 0 / 0          | 0 / 0          |  |
| <b>Hypomagnesaemia</b>   |                |                |  |

|   |                |                |
|---|----------------|----------------|
| subjects affected / exposed                     | 1 / 58 (1.72%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |

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

| <b>Non-serious adverse events</b>                     | Bendamustine      | Treatment of Physician's Choice (TPC) |
|---|-------------------|---------------------------------------|
| Total subjects affected by non-serious adverse events |                   |                                       |
| subjects affected / exposed                           | 58 / 58 (100.00%) | 27 / 27 (100.00%)                     |
| Investigations  |                   |                                       |
| Platelet count decreased                              |                   |                                       |
| subjects affected / exposed                           | 10 / 58 (17.24%)  | 3 / 27 (11.11%)                       |
| occurrences (all)                                     | 23                | 7                                     |
| Neutrophil count decreased                            |                   |                                       |
| subjects affected / exposed                           | 11 / 58 (18.97%)  | 1 / 27 (3.70%)                        |
| occurrences (all)                                     | 34                | 1                                     |
| Weight decreased                                      |                   |                                       |
| subjects affected / exposed                           | 6 / 58 (10.34%)   | 1 / 27 (3.70%)                        |
| occurrences (all)                                     | 8                 | 1                                     |
| White blood cell count decreased                      |                   |                                       |
| subjects affected / exposed                           | 5 / 58 (8.62%)    | 2 / 27 (7.41%)                        |
| occurrences (all)                                     | 13                | 4                                     |
| Blood alkaline phosphatase increased                  |                   |                                       |
| subjects affected / exposed                           | 1 / 58 (1.72%)    | 2 / 27 (7.41%)                        |
| occurrences (all)                                     | 1                 | 2                                     |
| Nervous system disorders                              |                   |                                       |
| Headache  |                   |                                       |
| subjects affected / exposed                           | 7 / 58 (12.07%)   | 2 / 27 (7.41%)                        |
| occurrences (all)                                     | 8                 | 3                                     |
| Dysgeusia   |                   |                                       |
| subjects affected / exposed                           | 6 / 58 (10.34%)   | 1 / 27 (3.70%)                        |
| occurrences (all)                                     | 6                 | 1                                     |
| Lethargy  |                   |                                       |
| subjects affected / exposed                           | 4 / 58 (6.90%)    | 3 / 27 (11.11%)                       |
| occurrences (all)                                     | 5                 | 3                                     |

|   |                        |                       |  |
|---|------------------------|-----------------------|--|
| Neuropathy peripheral<br>subjects affected / exposed<br>occurrences (all) | 4 / 58 (6.90%)<br>4    | 0 / 27 (0.00%)<br>0   |  |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)             | 3 / 58 (5.17%)<br>5    | 0 / 27 (0.00%)<br>0   |  |
| Presyncope<br>subjects affected / exposed<br>occurrences (all)            | 3 / 58 (5.17%)<br>3    | 0 / 27 (0.00%)<br>0   |  |
| General disorders and administration<br>site conditions                   |                        |                       |  |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)               | 27 / 58 (46.55%)<br>40 | 8 / 27 (29.63%)<br>10 |  |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)               | 5 / 58 (8.62%)<br>15   | 2 / 27 (7.41%)<br>2   |  |
| Oedema peripheral<br>subjects affected / exposed<br>occurrences (all)     | 8 / 58 (13.79%)<br>9   | 1 / 27 (3.70%)<br>2   |  |
| Asthenia<br>subjects affected / exposed<br>occurrences (all)              | 7 / 58 (12.07%)<br>10  | 0 / 27 (0.00%)<br>0   |  |
| Chills<br>subjects affected / exposed<br>occurrences (all)                | 5 / 58 (8.62%)<br>7    | 0 / 27 (0.00%)<br>0   |  |
| Blood and lymphatic system disorders                                      |                        |                       |  |
| Neutropenia<br>subjects affected / exposed<br>occurrences (all)           | 19 / 58 (32.76%)<br>45 | 8 / 27 (29.63%)<br>13 |  |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)               | 13 / 58 (22.41%)<br>31 | 5 / 27 (18.52%)<br>12 |  |
| Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all)      | 13 / 58 (22.41%)<br>36 | 4 / 27 (14.81%)<br>6  |  |
| Leukopenia  |                        |                       |  |

|  |                        |                      |  |
|--|------------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all)       | 0 / 58 (0.00%)<br>0    | 2 / 27 (7.41%)<br>4  |  |
| <b>Gastrointestinal disorders</b>                      |                        |                      |  |
| <b>Nausea</b>  |                        |                      |  |
| subjects affected / exposed<br>occurrences (all)       | 33 / 58 (56.90%)<br>50 | 9 / 27 (33.33%)<br>9 |  |
| <b>Constipation</b>                                    |                        |                      |  |
| subjects affected / exposed<br>occurrences (all)       | 27 / 58 (46.55%)<br>31 | 4 / 27 (14.81%)<br>4 |  |
| <b>Diarrhoea</b>                                       |                        |                      |  |
| subjects affected / exposed<br>occurrences (all)       | 18 / 58 (31.03%)<br>29 | 5 / 27 (18.52%)<br>7 |  |
| <b>Vomiting</b>  |                        |                      |  |
| subjects affected / exposed<br>occurrences (all)       | 14 / 58 (24.14%)<br>22 | 5 / 27 (18.52%)<br>5 |  |
| <b>Mouth ulceration</b>                                |                        |                      |  |
| subjects affected / exposed<br>occurrences (all)       | 9 / 58 (15.52%)<br>10  | 1 / 27 (3.70%)<br>1  |  |
| <b>Abdominal pain</b>                                  |                        |                      |  |
| subjects affected / exposed<br>occurrences (all)       | 4 / 58 (6.90%)<br>5    | 2 / 27 (7.41%)<br>2  |  |
| <b>Dry mouth</b>                                       |                        |                      |  |
| subjects affected / exposed<br>occurrences (all)       | 5 / 58 (8.62%)<br>6    | 1 / 27 (3.70%)<br>1  |  |
| <b>Gastrooesophageal reflux disease</b>                |                        |                      |  |
| subjects affected / exposed<br>occurrences (all)       | 6 / 58 (10.34%)<br>6   | 0 / 27 (0.00%)<br>0  |  |
| <b>Abdominal pain upper</b>                            |                        |                      |  |
| subjects affected / exposed<br>occurrences (all)       | 3 / 58 (5.17%)<br>3    | 1 / 27 (3.70%)<br>1  |  |
| <b>Stomatitis</b>                                      |                        |                      |  |
| subjects affected / exposed<br>occurrences (all)       | 3 / 58 (5.17%)<br>3    | 2 / 27 (7.41%)<br>3  |  |
| <b>Respiratory, thoracic and mediastinal disorders</b> |                        |                      |  |

|  |                        |                      |  |
|--|------------------------|----------------------|--|
| Cough<br>subjects affected / exposed<br>occurrences (all)              | 12 / 58 (20.69%)<br>15 | 5 / 27 (18.52%)<br>7 |  |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)           | 7 / 58 (12.07%)<br>8   | 0 / 27 (0.00%)<br>0  |  |
| Rhinitis allergic<br>subjects affected / exposed<br>occurrences (all)  | 3 / 58 (5.17%)<br>3    | 1 / 27 (3.70%)<br>1  |  |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all) | 3 / 58 (5.17%)<br>3    | 0 / 27 (0.00%)<br>0  |  |
| Skin and subcutaneous tissue disorders                                 |                        |                      |  |
| Rash<br>subjects affected / exposed<br>occurrences (all)               | 7 / 58 (12.07%)<br>8   | 2 / 27 (7.41%)<br>2  |  |
| Dry skin<br>subjects affected / exposed<br>occurrences (all)           | 5 / 58 (8.62%)<br>5    | 1 / 27 (3.70%)<br>1  |  |
| Pruritus<br>subjects affected / exposed<br>occurrences (all)           | 3 / 58 (5.17%)<br>4    | 0 / 27 (0.00%)<br>0  |  |
| Psychiatric disorders  |                        |                      |  |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)           | 5 / 58 (8.62%)<br>5    | 2 / 27 (7.41%)<br>2  |  |
| Anxiety<br>subjects affected / exposed<br>occurrences (all)            | 3 / 58 (5.17%)<br>4    | 1 / 27 (3.70%)<br>1  |  |
| Depression<br>subjects affected / exposed<br>occurrences (all)         | 1 / 58 (1.72%)<br>1    | 2 / 27 (7.41%)<br>2  |  |
| Musculoskeletal and connective tissue disorders                        |                        |                      |  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)  | 7 / 58 (12.07%)<br>7   | 1 / 27 (3.70%)<br>2  |  |

|   |                        |                      |  |
|---|------------------------|----------------------|--|
| Musculoskeletal pain<br>subjects affected / exposed<br>occurrences (all)    | 2 / 58 (3.45%)<br>6    | 1 / 27 (3.70%)<br>1  |  |
| Infections and infestations   |                        |                      |  |
| Oral candidiasis<br>subjects affected / exposed<br>occurrences (all)        | 8 / 58 (13.79%)<br>8   | 0 / 27 (0.00%)<br>0  |  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all) | 3 / 58 (5.17%)<br>3    | 2 / 27 (7.41%)<br>2  |  |
| Metabolism and nutrition disorders  |                        |                      |  |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)      | 14 / 58 (24.14%)<br>16 | 3 / 27 (11.11%)<br>3 |  |
| Hypokalaemia<br>subjects affected / exposed<br>occurrences (all)            | 8 / 58 (13.79%)<br>12  | 2 / 27 (7.41%)<br>2  |  |
| Hypomagnesaemia<br>subjects affected / exposed<br>occurrences (all)         | 6 / 58 (10.34%)<br>7   | 1 / 27 (3.70%)<br>1  |  |
| Hypoalbuminaemia<br>subjects affected / exposed<br>occurrences (all)        | 3 / 58 (5.17%)<br>6    | 0 / 27 (0.00%)<br>0  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date          | Amendment  |
|---------------|--|
| 08 April 2011 | The overall reason of this amendment was to update study design methodology. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

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

|  |
|--|
| The study did not achieve the recruitment goal and was therefore terminated early. |
|--|

Notes: