



## Clinical trial results:

### A Phase 2, Randomized Study of VELCADE® (Bortezomib), Dexamethasone, and Thalidomide Versus VELCADE® (Bortezomib), Dexamethasone, Thalidomide, and Cyclophosphamide in Subjects With Previously Untreated Multiple Myeloma Who Are Candidates for Autologous Transplantation

#### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2006-006050-10    |
| Trial protocol           | FR AT HU PT CZ IT |
| Global end of trial date | 16 October 2013   |

#### Results information

|                                |   |
|--------------------------------|---|
| Result version number          | v2 (current)                                    |
| This version publication date  | 23 June 2016                                    |
| First version publication date | 06 August 2015                                  |
| Version creation reason        | • Correction of full data set<br>Review of data |

#### Trial information

##### Trial identification

|                       |                 |
|-----------------------|-----------------|
| Sponsor protocol code | 26866138MMY2043 |
|-----------------------|-----------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00531453 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Janssen-Cilag International NV  |
| Sponsor organisation address | Turnhoutseweg 30, Beerse, Belgium, 2340   |
| Public contact               | Clinical Registry Group,, Janssen-Cilag International NV,<br>ClinicalTrialsEU@its.jnj.com |
| Scientific contact           | Clinical Registry Group, Janssen-Cilag International NV,<br>ClinicalTrialsEU@its.jnj.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                       | 16 October 2013 |
| Is this the analysis of the primary completion data? | No              |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 16 October 2013 |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study is to determine the overall combined complete response rate (CR rate) (defined in this protocol as the combination of complete response [CR, including sCR and nCR]) following induction treatment with VDT or VDTC in subjects with newly diagnosed symptomatic multiple myeloma who are candidates for HDT/SCT.

Protection of trial subjects:

All participating subjects received full supportive care and were followed closely for safety throughout the study. Safety assessments occur through regular clinic visits including laboratory analyses. Special attention was given to the early detection of neurotoxicity (through the FACT/GOG -Ntx questionnaire checklist, investigator assessment, and possibly assessments by a neurologist).

Background therapy: -

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 04 October 2007 |
| Long term follow-up planned                               | Yes             |
| Long term follow-up rationale                             | Safety          |
| Long term follow-up duration                              | 5 Years         |
| Independent data monitoring committee (IDMC) involvement? | No              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Austria: 20        |
| Country: Number of subjects enrolled | Czech Republic: 16 |
| Country: Number of subjects enrolled | France: 14         |
| Country: Number of subjects enrolled | Hungary: 9         |
| Country: Number of subjects enrolled | Israel: 7          |
| Country: Number of subjects enrolled | Italy: 6           |
| Country: Number of subjects enrolled | Poland: 10         |
| Country: Number of subjects enrolled | Portugal: 16       |
| Worldwide total number of subjects   | 98                 |
| EEA total number of subjects         | 91                 |

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)                      | 90 |
| From 65 to 84 years                       | 8  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

98 patients were enrolled between October 2007 and September 2008

### Pre-assignment

Screening details:

All enrolled patients received at least one dose of study drug.

### Period 1

|                              |                                       |
|------------------------------|---------------------------------------|
| Period 1 title               | Induction Cycles 1-4 (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> | Four Drug Regimen (VDTC) |
|------------------|--------------------------|

Arm description:

Treatment Group B (VDTC) - Cyclophosphamide 400 mg/m<sup>2</sup> IV on Days 1 and 8 in addition to the therapies described for Treatment Group A.

|  |                                   |
|--|-----------------------------------|
| Arm type                               | Experimental                      |
| Investigational medicinal product name | Velcade (bortezomib)              |
| Investigational medicinal product code |                                   |
| Other name                             |                                   |
| Pharmaceutical forms                   | Powder for solution for injection |
| Routes of administration               | Intravenous use                   |

Dosage and administration details:

Participants will receive velcade 1.3 milligram per meter square [mg/m<sup>2</sup>] as an intravenous (i.v.) bolus injection on Days 1,4,8, and 11, followed by a 10 day rest period (Days 12 to 21).

|  |                                   |
|--|-----------------------------------|
| Investigational medicinal product name | Dexamethasone                     |
| Investigational medicinal product code |                                   |
| Other name                             |                                   |
| Pharmaceutical forms                   | Powder for solution for injection |
| Routes of administration               | Intravenous use                   |

Dosage and administration details:

Dexamethasone 40 milligram per day (mg/day) was given orally by mouth (p.o.) on Days 1-4 and Days 9-12 in each of 4 cycles.

|  |             |
|--|-------------|
| Investigational medicinal product name | Thalidomide |
| Investigational medicinal product code |             |
| Other name                             |             |
| Pharmaceutical forms                   | Capsule     |
| Routes of administration               | Oral use    |

Dosage and administration details:

Thalidomide 100 milligram (mg) orally Every day, starting on Day 1 of Cycle 1 (e.g. the same day of the first dose of Velcade) and continuing until Day 21 of Cycle 4.

|  |                                   |
|--|-----------------------------------|
| Investigational medicinal product name | Cyclophosphamide                  |
| Investigational medicinal product code |                                   |
| Other name                             |                                   |
| Pharmaceutical forms                   | Powder for solution for injection |
| Routes of administration               | Intravenous use                   |

**Dosage and administration details:**

400 milligram per meter square [mg/m<sup>2</sup>] on Day 1 and Day 8 of each 3-week cycle, for a total of 4 cycles.

|                  |  |
|------------------|--|
| <b>Arm title</b> | Three Drug Regimen (VDT): Bortezomib, Dexamethasone, and Thali |
|------------------|--|

**Arm description:**

VELCADE (bortezomib) twice weekly for 4 cycles (4 doses per cycle), prior to high-dose chemotherapy (HDT) and stem cell transplantation(SCT). Subjects will receive VELCADE 1.3 mg/m<sup>2</sup> as an intravenous (i.v.) bolus injection on Days 1, 4, 8, and 11, followed by a 10 day rest period (Days 12 to 21). Dexamethasone 40 mg/day given by mouth on Days 1-4 and Days 9-12 in each of 4 cycles. Thalidomide given by mouth every day, starting on Day 1 of Cycle 1 (e.g. the same day of the first dose of VELCADE) and continuing until Day 21 of Cycle 4 at a dose of 100 mg/day (bedtime).

|  |                                   |
|--|-----------------------------------|
| Arm type                               | Experimental                      |
| Investigational medicinal product name | Velcade (bortezomib)              |
| Investigational medicinal product code |                                   |
| Other name                             |                                   |
| Pharmaceutical forms                   | Powder for solution for injection |
| Routes of administration               | Intravenous use                   |

**Dosage and administration details:**

VELCADE (bortezomib) twice weekly for 4 cycles (4 doses per cycle), prior to high-dose chemotherapy (HDT) and stem cell transplantation(SCT). Subjects received VELCADE 1.3 mg/m<sup>2</sup> as an intravenous (i.v.) bolus injection on Days 1, 4, 8, and 11, followed by a 10 day rest period (Days 12 to 21).

|  |                                   |
|--|-----------------------------------|
| Investigational medicinal product name | Dexamethasone                     |
| Investigational medicinal product code |                                   |
| Other name                             |                                   |
| Pharmaceutical forms                   | Powder for solution for injection |
| Routes of administration               | Intravenous use                   |

**Dosage and administration details:**

Dexamethasone 40 milligram per day (mg/day) was given orally by mouth (p.o.) on Days 1-4 and Days 9-12 in each of 4 cycles.

|  |             |
|--|-------------|
| Investigational medicinal product name | Thalidomide |
| Investigational medicinal product code |             |
| Other name                             |             |
| Pharmaceutical forms                   | Capsule     |
| Routes of administration               | Oral use    |

**Dosage and administration details:**

Thalidomide 100 milligram (mg) orally Every day, starting on Day 1 of Cycle 1 (e.g. the same day of the first dose of Velcade) and continuing until Day 21 of Cycle 4.

| Number of subjects in period 1 | Four Drug Regimen (VDTC) | Three Drug Regimen (VDT): Bortezomib, Dexamethasone, and Thali |
|--------------------------------|--------------------------|--|
|                                |                          |  |
| Started                        | 49                       | 49   |
| Completed                      | 45                       | 46   |
| Not completed                  | 4                        | 3  |
| Adverse event, serious fatal   | 1                        | -  |

|                                  |   |   |
|----------------------------------|---|---|
| Adverse event, non-fatal         | - | 1 |
| Adverse event, serious non-fatal | 2 | 2 |
| Lack of efficacy                 | 1 | - |

## Baseline characteristics

### Reporting groups

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | Four Drug Regimen (VDTC) |
|-----------------------|--------------------------|

Reporting group description:

Treatment Group B (VDTC) - Cyclophosphamide 400 mg/m<sup>2</sup> IV on Days 1 and 8 in addition to the therapies described for Treatment Group A.

|                       |  |
|-----------------------|--|
| Reporting group title | Three Drug Regimen (VDT): Bortezomib, Dexamethasone, and Thali |
|-----------------------|--|

Reporting group description:

VELCADE (bortezomib) twice weekly for 4 cycles (4 doses per cycle), prior to high-dose chemotherapy (HDT) and stem cell transplantation(SCT). Subjects will receive VELCADE 1.3 mg/m<sup>2</sup> as an intravenous (i.v.) bolus injection on Days 1, 4, 8, and 11, followed by a 10 day rest period (Days 12 to 21). Dexamethasone 40 mg/day given by mouth on Days 1-4 and Days 9-12 in each of 4 cycles. Thalidomide given by mouth every day, starting on Day 1 of Cycle 1 (e.g. the same day of the first dose of VELCADE) and continuing until Day 21 of Cycle 4 at a dose of 100 mg/day (bedtime).

| Reporting group values                      | Four Drug Regimen (VDTC) | Three Drug Regimen (VDT): Bortezomib, Dexamethasone, and Thali | Total |
|---|--------------------------|--|-------|
| Number of subjects                          | 49                       | 49   | 98    |
| Title for AgeCategorical<br>Units: subjects |                          |  |       |
| Children (2-11 years)                       | 0                        | 0  | 0     |
| Adolescents (12-17 years)                   | 0                        | 0  | 0     |
| Adults (18-64 years)                        | 44                       | 46   | 90    |
| From 65 to 84 years                         | 5                        | 3  | 8     |
| 85 years and over                           | 0                        | 0  | 0     |
| Title for AgeContinuous<br>Units: years     |                          |  |       |
| arithmetic mean                             | 55.8                     | 55.1   | -     |
| standard deviation                          | ± 8.27                   | ± 7.04   | -     |
| Title for Gender<br>Units: subjects         |                          |  |       |
| Female                                      | 24                       | 23   | 47    |
| Male  | 25                       | 26   | 51    |

## End points

### End points reporting groups

|   |  |
|---|--|
| Reporting group title   | Four Drug Regimen (VDTC)                                       |
| Reporting group description:<br>Treatment Group B (VDTC) - Cyclophosphamide 400 mg/m <sup>2</sup> IV on Days 1 and 8 in addition to the therapies described for Treatment Group A.  |  |
| Reporting group title   | Three Drug Regimen (VDT): Bortezomib, Dexamethasone, and Thali |
| Reporting group description:<br>VELCADE (bortezomib) twice weekly for 4 cycles (4 doses per cycle), prior to high-dose chemotherapy (HDT) and stem cell transplantation(SCT). Subjects will receive VELCADE 1.3 mg/m <sup>2</sup> as an intravenous (i.v.) bolus injection on Days 1, 4, 8, and 11, followed by a 10 day rest period (Days 12 to 21). Dexamethasone 40 mg/day given by mouth on Days 1-4 and Days 9-12 in each of 4 cycles. Thalidomide given by mouth every day, starting on Day 1 of Cycle 1 (e.g. the same day of the first dose of VELCADE) and continuing until Day 21 of Cycle 4 at a dose of 100 mg/day (bedtime). |  |

### Primary: Percentage of Participants Achieving Overall Combined Complete Response (CR) Following Induction

|   |  |
|---|--|
| End point title   | Percentage of Participants Achieving Overall Combined Complete Response (CR) Following Induction |
| End point description:<br>Percent of Participants Achieving Overall combined complete response (CR w/normalized serum kappa: lambda ratio + CR + near complete response [nCR]) following induction therapy: CR criteria: negative immunofixation on the serum and urine, disappearance of any soft tissue plasmacytomas and less than <5 percent (%) plasma cells in bone marrow; kappa: lambda ratio: normal free light chain (FLC) ratio; nCR criteria: positive immunofixation analysis of serum or urine as the only evidence of disease; disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow. |  |
| End point type  | Primary  |
| End point timeframe:<br>Cycle 1 up to Cycle 4/8 up to End-of-Induction Treatment Visit/ End-of-Extension Treatment Visit (30 days after the last dose of study drugs )  |  |

| End point values                  | Four Drug Regimen (VDTC) | Three Drug Regimen (VDT): Bortezomib, Dexamethasone, and Thali |  |  |
|-----------------------------------|--------------------------|--|--|--|
| Subject group type                | Reporting group          | Reporting group  |  |  |
| Number of subjects analysed       | 49                       | 48   |  |  |
| Units: percentage of participants |                          |  |  |  |
| number (confidence interval 95%)  | 43.75 (29.5 to 58.8)     | 51.02 (36.3 to 65.6)   |  |  |



## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Statistical Analysis  |
| Comparison groups                       | Four Drug Regimen (VDTC) v Three Drug Regimen (VDT): Bortezomib, Dexamethasone, and Thali |
| Number of subjects included in analysis | 97  |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | equivalence   |
| P-value                                 | = 0.5056  |
| Method                                  | Stratified Log rank test  |

## Secondary: Percentage of Participants Achieving Overall Combined Complete Response (CR) Following High-dose Chemotherapy (HDT)/Stem Cell Transplantation (SCT)

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants Achieving Overall Combined Complete Response (CR) Following High-dose Chemotherapy (HDT)/Stem Cell Transplantation (SCT) |
|-----------------|---|

### End point description:

Percent of Participants Achieving Overall Combined Complete Response (CR) (CR w/normalized serum kappa: lambda ratio + CR + Near Complete Response [nCR]) following stem cell transplantation. CR criteria: negative immunofixation on the serum and urine, disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow. kappa:lambda ratio: normal free light chain (FLC) ratio. nCR criteria: positive immunofixation analysis of serum or urine as the only evidence of disease; disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow.

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

### End point timeframe:

Cycle 1 up to Cycle 4/8 up to End-of-Induction Treatment Visit/ End-of-Extension Treatment Visit (30 days after the last dose of study drugs )

| <b>End point values</b>           | Four Drug Regimen (VDTC) | Three Drug Regimen (VDT): Bortezomib, Dexamethasone, and Thali |  |  |
|-----------------------------------|--------------------------|--|--|--|
| Subject group type                | Reporting group          | Reporting group  |  |  |
| Number of subjects analysed       | 38                       | 27   |  |  |
| Units: Percentage of Participants |                          |  |  |  |
| number (confidence interval 95%)  | 77.78 (57.7 to 91.4)     | 76.32 (59.8 to 88.6)   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From first dose to 30 days post last dose

Adverse event reporting additional description:

Treatment emergent

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 11.1 |
|--------------------|------|

### Reporting groups

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | VDTC (Treatment Group B) |
|-----------------------|--------------------------|

Reporting group description:

Treatment Group B (VDTC) - Cyclophosphamide 400 mg/m<sup>2</sup> IV on Days 1 and 8 in addition to the therapies described for Treatment Group A.

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | VDT (Treatment Group A) |
|-----------------------|-------------------------|

Reporting group description:

Treatment Group A (VDT) - VELCADE 1.3 mg/m<sup>2</sup> intravenously (IV) on Days 1, 4, 8, and 11, Dexamethasone 40 mg orally on Days 1 to 4 and Days 9 to 12, and Thalidomide 100 mg orally every day beginning on Day 1 of Cycle 1 until Day 21 of Cycle 4.

| Serious adverse events                               | VDTC (Treatment Group B) | VDT (Treatment Group A) |  |
|--|--------------------------|-------------------------|--|
| Total subjects affected by serious adverse events    |                          |                         |  |
| subjects affected / exposed                          | 20 / 49 (40.82%)         | 11 / 49 (22.45%)        |  |
| number of deaths (all causes)                        | 2                        | 2                       |  |
| number of deaths resulting from adverse events       | 1                        | 0                       |  |
| Vascular disorders                                   |                          |                         |  |
| Thrombosis   |                          |                         |  |
| subjects affected / exposed                          | 1 / 49 (2.04%)           | 0 / 49 (0.00%)          |  |
| occurrences causally related to treatment / all      | 1 / 1                    | 0 / 0                   |  |
| deaths causally related to treatment / all           | 0 / 0                    | 0 / 0                   |  |
| General disorders and administration site conditions |                          |                         |  |
| Acute Phase Reaction                                 |                          |                         |  |
| subjects affected / exposed                          | 1 / 49 (2.04%)           | 0 / 49 (0.00%)          |  |
| occurrences causally related to treatment / all      | 0 / 1                    | 0 / 0                   |  |
| deaths causally related to treatment / all           | 0 / 0                    | 0 / 0                   |  |
| Chest Pain   |                          |                         |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 2 / 49 (4.08%) | 0 / 49 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Fatigue   |                |                |  |
| subjects affected / exposed                     | 2 / 49 (4.08%) | 1 / 49 (2.04%) |  |
| occurrences causally related to treatment / all | 2 / 2          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Generalised Oedema                              |                |                |  |
| subjects affected / exposed                     | 0 / 49 (0.00%) | 1 / 49 (2.04%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Oedema Peripheral                               |                |                |  |
| subjects affected / exposed                     | 1 / 49 (2.04%) | 2 / 49 (4.08%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 1 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pyrexia   |                |                |  |
| subjects affected / exposed                     | 1 / 49 (2.04%) | 0 / 49 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Respiratory, thoracic and mediastinal disorders |                |                |  |
| Dyspnoea  |                |                |  |
| subjects affected / exposed                     | 1 / 49 (2.04%) | 2 / 49 (4.08%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Epistaxis                                       |                |                |  |
| subjects affected / exposed                     | 1 / 49 (2.04%) | 0 / 49 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Lung Disorder                                   |                |                |  |
| subjects affected / exposed                     | 1 / 49 (2.04%) | 0 / 49 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Lung Infiltration                               |                |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 1 / 49 (2.04%) | 0 / 49 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pleural Effusion                                |                |                |  |
| subjects affected / exposed                     | 0 / 49 (0.00%) | 1 / 49 (2.04%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Psychiatric disorders                           |                |                |  |
| Panic Attack                                    |                |                |  |
| subjects affected / exposed                     | 1 / 49 (2.04%) | 0 / 49 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Injury, poisoning and procedural complications  |                |                |  |
| Femoral Neck Fracture                           |                |                |  |
| subjects affected / exposed                     | 1 / 49 (2.04%) | 0 / 49 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pubic Rami Fracture                             |                |                |  |
| subjects affected / exposed                     | 1 / 49 (2.04%) | 0 / 49 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Spinal Fracture                                 |                |                |  |
| subjects affected / exposed                     | 1 / 49 (2.04%) | 0 / 49 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Cardiac disorders                               |                |                |  |
| Angina Pectoris                                 |                |                |  |
| subjects affected / exposed                     | 1 / 49 (2.04%) | 0 / 49 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Atrial Fibrillation                             |                |                |  |
| subjects affected / exposed                     | 0 / 49 (0.00%) | 1 / 49 (2.04%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

|   |                |                |  |
|---|----------------|----------------|--|
| Cardio-Respiratory Arrest                       |                |                |  |
| subjects affected / exposed                     | 1 / 49 (2.04%) | 0 / 49 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all      | 1 / 1          | 0 / 0          |  |
| Nervous system disorders                        |                |                |  |
| Autonomic Neuropathy                            |                |                |  |
| subjects affected / exposed                     | 0 / 49 (0.00%) | 1 / 49 (2.04%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Dizziness                                       |                |                |  |
| subjects affected / exposed                     | 1 / 49 (2.04%) | 0 / 49 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Neuropathy Peripheral                           |                |                |  |
| subjects affected / exposed                     | 0 / 49 (0.00%) | 1 / 49 (2.04%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Peripheral Sensory Neuropathy                   |                |                |  |
| subjects affected / exposed                     | 0 / 49 (0.00%) | 2 / 49 (4.08%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 2 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Sciatica  |                |                |  |
| subjects affected / exposed                     | 1 / 49 (2.04%) | 0 / 49 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Blood and lymphatic system disorders            |                |                |  |
| Anaemia   |                |                |  |
| subjects affected / exposed                     | 2 / 49 (4.08%) | 1 / 49 (2.04%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Gastrointestinal disorders                      |                |                |  |
| Abdominal Pain                                  |                |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 1 / 49 (2.04%) | 0 / 49 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Constipation                                    |                |                |  |
| subjects affected / exposed                     | 2 / 49 (4.08%) | 2 / 49 (4.08%) |  |
| occurrences causally related to treatment / all | 1 / 2          | 2 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Diarrhoea                                       |                |                |  |
| subjects affected / exposed                     | 1 / 49 (2.04%) | 1 / 49 (2.04%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Dyspepsia                                       |                |                |  |
| subjects affected / exposed                     | 1 / 49 (2.04%) | 0 / 49 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Faecal Vomiting                                 |                |                |  |
| subjects affected / exposed                     | 0 / 49 (0.00%) | 1 / 49 (2.04%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Vomiting  |                |                |  |
| subjects affected / exposed                     | 0 / 49 (0.00%) | 1 / 49 (2.04%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Skin and subcutaneous tissue disorders          |                |                |  |
| Toxic Skin Eruption                             |                |                |  |
| subjects affected / exposed                     | 1 / 49 (2.04%) | 0 / 49 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Renal and urinary disorders                     |                |                |  |
| Urinary Incontinence                            |                |                |  |
| subjects affected / exposed                     | 0 / 49 (0.00%) | 1 / 49 (2.04%) |  |
| 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                                       |                |                |  |
| Arthralgia                                      |                |                |  |
| subjects affected / exposed                     | 2 / 49 (4.08%) | 0 / 49 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Back Pain                                       |                |                |  |
| subjects affected / exposed                     | 3 / 49 (6.12%) | 1 / 49 (2.04%) |  |
| occurrences causally related to treatment / all | 0 / 6          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Bone Pain                                       |                |                |  |
| subjects affected / exposed                     | 2 / 49 (4.08%) | 0 / 49 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Musculoskeletal Pain                            |                |                |  |
| subjects affected / exposed                     | 1 / 49 (2.04%) | 0 / 49 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Neck Pain                                       |                |                |  |
| subjects affected / exposed                     | 1 / 49 (2.04%) | 0 / 49 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pain in Extremity                               |                |                |  |
| subjects affected / exposed                     | 1 / 49 (2.04%) | 0 / 49 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Infections and infestations                     |                |                |  |
| Bronchopneumonia                                |                |                |  |
| subjects affected / exposed                     | 1 / 49 (2.04%) | 1 / 49 (2.04%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Clostridium Difficile Colitis                   |                |                |  |
| subjects affected / exposed                     | 1 / 49 (2.04%) | 0 / 49 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

|   |                |                |  |
|---|----------------|----------------|--|
| Bronchopulmonary Aspergillosis                  |                |                |  |
| subjects affected / exposed                     | 1 / 49 (2.04%) | 0 / 49 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Escherichia Sepsis                              |                |                |  |
| subjects affected / exposed                     | 0 / 49 (0.00%) | 1 / 49 (2.04%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Fungal Sepsis                                   |                |                |  |
| subjects affected / exposed                     | 1 / 49 (2.04%) | 0 / 49 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Herpes Zoster                                   |                |                |  |
| subjects affected / exposed                     | 1 / 49 (2.04%) | 0 / 49 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pneumonia                                       |                |                |  |
| subjects affected / exposed                     | 2 / 49 (4.08%) | 1 / 49 (2.04%) |  |
| occurrences causally related to treatment / all | 2 / 2          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Sinusitis                                       |                |                |  |
| subjects affected / exposed                     | 1 / 49 (2.04%) | 0 / 49 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Metabolism and nutrition disorders              |                |                |  |
| Fluid Retention                                 |                |                |  |
| subjects affected / exposed                     | 1 / 49 (2.04%) | 0 / 49 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Dehydration                                     |                |                |  |
| subjects affected / exposed                     | 0 / 49 (0.00%) | 1 / 49 (2.04%) |  |
| 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: 5 %

| <b>Non-serious adverse events</b>                     | <b>VDTC (Treatment Group B)</b> | <b>VDT (Treatment Group A)</b> |  |
|---|---------------------------------|--------------------------------|--|
| Total subjects affected by non-serious adverse events |                                 |                                |  |
| subjects affected / exposed                           | 44 / 49 (89.80%)                | 48 / 49 (97.96%)               |  |
| Vascular disorders                                    |                                 |                                |  |
| Hypertension  |                                 |                                |  |
| subjects affected / exposed                           | 6 / 49 (12.24%)                 | 3 / 49 (6.12%)                 |  |
| occurrences (all)                                     | 6                               | 3                              |  |
| Hypotension   |                                 |                                |  |
| subjects affected / exposed                           | 4 / 49 (8.16%)                  | 1 / 49 (2.04%)                 |  |
| occurrences (all)                                     | 5                               | 1                              |  |
| General disorders and administration site conditions  |                                 |                                |  |
| Asthenia  |                                 |                                |  |
| subjects affected / exposed                           | 7 / 49 (14.29%)                 | 10 / 49 (20.41%)               |  |
| occurrences (all)                                     | 8                               | 15                             |  |
| Face Oedema   |                                 |                                |  |
| subjects affected / exposed                           | 0 / 49 (0.00%)                  | 3 / 49 (6.12%)                 |  |
| occurrences (all)                                     | 0                               | 3                              |  |
| Fatigue   |                                 |                                |  |
| subjects affected / exposed                           | 10 / 49 (20.41%)                | 5 / 49 (10.20%)                |  |
| occurrences (all)                                     | 27                              | 8                              |  |
| Oedema  |                                 |                                |  |
| subjects affected / exposed                           | 6 / 49 (12.24%)                 | 4 / 49 (8.16%)                 |  |
| occurrences (all)                                     | 7                               | 5                              |  |
| Oedema Peripheral                                     |                                 |                                |  |
| subjects affected / exposed                           | 17 / 49 (34.69%)                | 16 / 49 (32.65%)               |  |
| occurrences (all)                                     | 25                              | 20                             |  |
| Pyrexia   |                                 |                                |  |
| subjects affected / exposed                           | 12 / 49 (24.49%)                | 6 / 49 (12.24%)                |  |
| occurrences (all)                                     | 15                              | 8                              |  |
| Respiratory, thoracic and mediastinal disorders       |                                 |                                |  |
| Cough   |                                 |                                |  |
| subjects affected / exposed                           | 3 / 49 (6.12%)                  | 4 / 49 (8.16%)                 |  |
| occurrences (all)                                     | 3                               | 4                              |  |

|   |                        |                        |  |
|---|------------------------|------------------------|--|
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)  | 2 / 49 (4.08%)<br>2    | 3 / 49 (6.12%)<br>3    |  |
| Psychiatric disorders<br>Insomnia<br>subjects affected / exposed<br>occurrences (all)               | 3 / 49 (6.12%)<br>3    | 5 / 49 (10.20%)<br>8   |  |
| Anxiety<br>subjects affected / exposed<br>occurrences (all)   | 0 / 49 (0.00%)<br>0    | 5 / 49 (10.20%)<br>5   |  |
| Investigations<br>Weight Increased<br>subjects affected / exposed<br>occurrences (all)              | 3 / 49 (6.12%)<br>4    | 2 / 49 (4.08%)<br>2    |  |
| Nervous system disorders<br>Dysgeusia<br>subjects affected / exposed<br>occurrences (all)           | 3 / 49 (6.12%)<br>4    | 1 / 49 (2.04%)<br>1    |  |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)                                    | 11 / 49 (22.45%)<br>15 | 11 / 49 (22.45%)<br>16 |  |
| Neuropathy Peripheral<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 49 (0.00%)<br>0    | 4 / 49 (8.16%)<br>5    |  |
| Peripheral Motor Neuropathy<br>subjects affected / exposed<br>occurrences (all)                     | 3 / 49 (6.12%)<br>10   | 3 / 49 (6.12%)<br>4    |  |
| Somnolence<br>subjects affected / exposed<br>occurrences (all)                                      | 0 / 49 (0.00%)<br>0    | 4 / 49 (8.16%)<br>4    |  |
| Peripheral Sensory Neuropathy<br>subjects affected / exposed<br>occurrences (all)                   | 12 / 49 (24.49%)<br>16 | 11 / 49 (22.45%)<br>19 |  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all) | 17 / 49 (34.69%)<br>37 | 7 / 49 (14.29%)<br>16  |  |

|  |                        |                        |  |
|--|------------------------|------------------------|--|
| Leukopenia<br>subjects affected / exposed<br>occurrences (all)                                   | 4 / 49 (8.16%)<br>11   | 0 / 49 (0.00%)<br>0    |  |
| Lymphopenia<br>subjects affected / exposed<br>occurrences (all)                                  | 5 / 49 (10.20%)<br>25  | 7 / 49 (14.29%)<br>16  |  |
| Neutropenia<br>subjects affected / exposed<br>occurrences (all)                                  | 8 / 49 (16.33%)<br>17  | 7 / 49 (14.29%)<br>8   |  |
| Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all)                             | 7 / 49 (14.29%)<br>14  | 4 / 49 (8.16%)<br>8    |  |
| Ear and labyrinth disorders<br>Vertigo<br>subjects affected / exposed<br>occurrences (all)       | 3 / 49 (6.12%)<br>4    | 2 / 49 (4.08%)<br>2    |  |
| Eye disorders<br>Conjunctivitis<br>subjects affected / exposed<br>occurrences (all)              | 3 / 49 (6.12%)<br>4    | 2 / 49 (4.08%)<br>2    |  |
| Vision Blurred<br>subjects affected / exposed<br>occurrences (all)                               | 3 / 49 (6.12%)<br>3    | 1 / 49 (2.04%)<br>1    |  |
| Gastrointestinal disorders<br>Abdominal Pain<br>subjects affected / exposed<br>occurrences (all) | 0 / 49 (0.00%)<br>0    | 3 / 49 (6.12%)<br>5    |  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)                                 | 24 / 49 (48.98%)<br>30 | 27 / 49 (55.10%)<br>34 |  |
| Abdominal Pain Upper<br>subjects affected / exposed<br>occurrences (all)                         | 2 / 49 (4.08%)<br>2    | 4 / 49 (8.16%)<br>4    |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                                    | 8 / 49 (16.33%)<br>12  | 4 / 49 (8.16%)<br>5    |  |
| Nausea   |                        |                        |  |

|  |   |   |  |
|--|---|---|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>9 / 49 (18.37%)</p> <p>16</p>  | <p>5 / 49 (10.20%)</p> <p>8</p>   |  |
| <p>Dyspepsia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>3 / 49 (6.12%)</p> <p>3</p>  | <p>3 / 49 (6.12%)</p> <p>4</p>  |  |
| <p>Stomatitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>4 / 49 (8.16%)</p> <p>4</p>  | <p>1 / 49 (2.04%)</p> <p>1</p>  |  |
| <p>Vomiting</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>4 / 49 (8.16%)</p> <p>6</p>  | <p>2 / 49 (4.08%)</p> <p>2</p>  |  |
| <p>Hepatobiliary disorders</p> <p>Hepatic Function Abnormal</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>2 / 49 (4.08%)</p> <p>2</p>  | <p>5 / 49 (10.20%)</p> <p>9</p>   |  |
| <p>Skin and subcutaneous tissue disorders</p> <p>Rash</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>3 / 49 (6.12%)</p> <p>5</p>  | <p>9 / 49 (18.37%)</p> <p>12</p>  |  |
| <p>Musculoskeletal and connective tissue disorders</p> <p>Bone Pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Back Pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pain in Extremity</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Muscle Spasms</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>6 / 49 (12.24%)</p> <p>7</p> <p>2 / 49 (4.08%)</p> <p>2</p> <p>5 / 49 (10.20%)</p> <p>5</p> <p>1 / 49 (2.04%)</p> <p>1</p> | <p>4 / 49 (8.16%)</p> <p>4</p> <p>4 / 49 (8.16%)</p> <p>4</p> <p>4 / 49 (8.16%)</p> <p>4</p> <p>3 / 49 (6.12%)</p> <p>5</p> |  |
| <p>Infections and infestations</p> <p>Oral Candidiasis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>0 / 49 (0.00%)</p> <p>0</p>  | <p>3 / 49 (6.12%)</p> <p>3</p>  |  |

|  |                       |                       |  |
|--|-----------------------|-----------------------|--|
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)    | 3 / 49 (6.12%)<br>5   | 3 / 49 (6.12%)<br>4   |  |
| Metabolism and nutrition disorders                                     |                       |                       |  |
| Anorexia<br>subjects affected / exposed<br>occurrences (all)           | 6 / 49 (12.24%)<br>8  | 3 / 49 (6.12%)<br>3   |  |
| Enzyme Abnormality<br>subjects affected / exposed<br>occurrences (all) | 3 / 49 (6.12%)<br>9   | 5 / 49 (10.20%)<br>15 |  |
| Hyperglycaemia<br>subjects affected / exposed<br>occurrences (all)     | 2 / 49 (4.08%)<br>18  | 5 / 49 (10.20%)<br>27 |  |
| Hyperuricaemia<br>subjects affected / exposed<br>occurrences (all)     | 0 / 49 (0.00%)<br>0   | 4 / 49 (8.16%)<br>4   |  |
| Hypoalbuminaemia<br>subjects affected / exposed<br>occurrences (all)   | 3 / 49 (6.12%)<br>6   | 1 / 49 (2.04%)<br>1   |  |
| Hypocalcaemia<br>subjects affected / exposed<br>occurrences (all)      | 6 / 49 (12.24%)<br>13 | 1 / 49 (2.04%)<br>1   |  |
| Hyponatraemia<br>subjects affected / exposed<br>occurrences (all)      | 3 / 49 (6.12%)<br>7   | 2 / 49 (4.08%)<br>3   |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date         | Amendment   |
|--------------|---|
| 21 June 2010 | The overall reason for the amendment was : Tto stop central testing of efficacy assessments, but continue to collect data related to time to progression and other efficacy parameters as routinely done by the investigator. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported